MEMORANDUM

To: Timothy Leighton, EPA; Bob Ross, Summitec Inc.; Andrew Yin, Summitec Inc.

From: Jonathan Cohen, ICF International, Inc.

Date: August 31, 2015

Re: Contract No.: EP-W-11-014 TAF 4-8-4:
AEATF Liquid Pour Study Statistical Analysis Review EPA and HSRB Comments

1. Introduction and Summary

In August 2012, AEATF submitted the final report for their study "A Study for Measurement of Potential Dermal and Inhalation Exposure during Application of a Liquid Antimicrobial Pesticide Product During Manual Pouring of a Liquid Containing an AntiMicrobial." Under previous Task Orders, ICF International, Inc. (ICF) analyzed the data from this study to investigate the relationship between dermal and inhalation exposures and the pesticide product usage, and helped EPA present the results of the analyses to the HSRB. Three scenarios were identified for this study: Conventional, pouring liquids from a conventional container into buckets or troughs; Reduced Splash, pouring liquids from a reduced splash container into buckets or troughs, and; Bottle, pouring liquids from a conventional or reduced splash container into a trigger spray bottle. Based on the results of the main study, EPA requested, and AEATF sponsored, a supplemental study "Supplemental Report 2" to collect additional dermal (hands only) and inhalation exposure data for the Bottle scenario. The supplemental study was submitted to EPA in May, 2015. ICF was asked by EPA through Summitec Inc. to analyze the combined Bottle scenario data from the original and supplemental study to investigate the relationship between dermal (hands only) and inhalation exposures and the pesticide product usage when pouring liquids into trigger spray bottles. Note that much of the SAS code used for these analyses and some of the following description was adapted from Sarkar's SAS code (which, in turn, was based on code provided by the AHETF) and his June 2010 Statistical Review "Review of Statistical Analyses in Agricultural Handler Exposure Task Force (AHETF) Monographs."

The report for the main study describes the experimental study methodology and the measurements in detail. Briefly, the study was carried out at an indoor test site in Concord, Ohio. Each of 18 volunteer subjects performed both the following scripted Conventional Pour study and the following scripted Reduced Splash study, in a randomly selected order.

For the Conventional Pour (CP) study, 18 volunteer subjects, referred to here as "workers," were randomly assigned into three groups of six subjects, numbered 1, 2 and 3, and the workers in group 1 were randomly assigned into two groups of three subjects, referred to as groups 1a and 1b. The workers in group 1a were assigned a task of pouring a liquid containing the active ingredient DDAC, diluted to approximately 0.2% active ingredient, from a set of 10 conventional small source containers of sizes 24, 32, and 64 fl oz into 32 fl oz trigger spray bottles, pouring 4 fl oz into each bottle. The workers in group 1b were assigned a task of pouring a liquid containing the active ingredient DDAC from a set of 10 conventional small source containers of sizes 24, 32, and 64 fl oz into 2 gallon buckets. The workers in group 2 were assigned a task of pouring a liquid containing the active ingredient DDAC from a set of 10 conventional medium source containers of sizes 128, 202, and 256 fl oz into either 2 gallon buckets, 4 gallon buckets, or 50 gallon low-walled troughs, where the three receiver container types were each randomly assigned to two of the group 1 workers. The workers in group 3 were assigned a task of pouring a liquid containing the active ingredient DDAC from a set of conventional large source containers of sizes 640 fl oz (5 gallon buckets) with standard flat lids into 50 gallon low-walled troughs. All subjects in group 1 and 4 randomly selected subjects in group 2 used a measuring cup. For each subject in groups 1 and 2, it was randomly determined whether the receiving containers would be placed on the floor or on a table (at waist to chest height). For all subjects in group 3, the receiving containers were on the floor. The analyses in this memorandum use the hand wash and air sampling data from the three workers in group 1a.

For the Reduced Splash (RS) study, the same 18 volunteer subjects, referred to here as "workers," were randomly assigned into three groups of six subjects, numbered 1, 2 and 3, and the workers in group 1 were randomly assigned into two groups of three subjects, referred to as groups 1a and 1b. All these assignments were independent of the Conventional Pour study assignments, so that a worker might not be in the same groups for the CP and RS studies.

The workers in group 1a were assigned a task of pouring a liquid containing the active ingredient C14 ADBAC, diluted to approximately 0.2% active ingredient, from a set of 10 reduced splash small source containers of size 64 fl oz into 32 fl oz trigger spray bottles, pouring 4 fl oz into each bottle. The workers in group 1b were assigned a task of pouring a liquid containing the active ingredient C14 ADBAC from a set of 10 reduced splash small source containers of size 64 fl oz into 2 gallon buckets. The workers in group 2 were assigned a task of pouring a liquid containing the active ingredient C14 ADBAC from a set of 10 reduced splash medium source containers of sizes 96, 128 and 180 fl oz into either 2 gallon buckets, 4 gallon buckets, or 50 gallon low-walled troughs, where the three receiver container types were each randomly assigned to two of the group 1 workers. The workers in group 3 were assigned a task of pouring a liquid containing the active ingredient C14 ADBAC from a set of large source containers of sizes 640 fl oz (5 gallon buckets) that had lids with a pull-out pour spout into 50 gallon low-walled troughs. All subjects in group 1, and 4 randomly selected subjects in group 2, used a measuring cup. For each subject in groups 1 and 2, it was randomly determined whether the receiving containers would be placed on the floor or on a table (at waist to chest height). For all subjects in group 3, the receiving containers were on the floor. The analyses in this memorandum use the hand wash and air sampling data from the three workers in group 1a. Note that one of these three workers was also a subject in group 1a of the Conventional Pour study. The statistical analyses in this memorandum do not make any adjustments to account for possible dependence between the two sets of measurements for that worker. Thus we will refer to six workers and six MEs from the original Bottle study even though it is more precise to say that there were five workers and six MEs.

Each subject was given inner and outer dosimeters to wear and was also given a personal air-sampling pump attached to an OVS air sampling tube. The air sampling pump was switched on at the beginning of the first monitoring experiment (ME) and turned off once the pouring was completed. The subject sat on a chair covered with plastic sheeting until the preparation of the containers for the second ME was completed. Then the air sampling pump was switched on again for the second ME and turned off once the pouring was completed. The air sampling tubes, hand wash, face/neck wipes, outer dosimeters, and inner dosimeters, were collected by a researcher and were later analyzed by the laboratory to measure the mass of DDAC

(attributable to the Conventional Pour active ingredient) and the mass of C14 ADBAC (attributable to the Reduced Splash active ingredient).

For the Supplemental Study, carried out in 2014, an additional group of 12 volunteer subjects, referred to here as "workers," was recruited. These 12 workers were assigned a task of pouring a liquid containing the active ingredient DDAC from a set of 10 conventional small source containers of sizes 16, 32, and 64 fl oz into 32 fl oz trigger spray bottles, pouring 4 fl oz into each bottle. All 12 subjects used a measuring cup. Based on recommendations from the HSRB during the January, 2013 board meeting, the concentration of DDAC was 0.2% for six workers and 0.02% for the other six workers. This study took place at the same location as the original 2012 study. Since the original study data showed that about 98% of the dermal exposure was to the hands, inner and outer dosimeters were not worn for the Supplemental Study; the workers wore their own clothes. Each subject was given a personal air-sampling pump attached to an OVS air sampling tube. The air sampling pump was switched on at the beginning of the monitoring experiment (ME) and turned off once the pouring was completed. The air sampling tubes and hand washes were collected by a researcher and were later analyzed by the laboratory to measure the mass of the active ingredient DDAC.

The exposure measurements in the report were corrected for the average percentage recovery of field fortification samples and for the removal efficiency of hand wash (90%) wipe samples. These analyses used the corrected measurements. An Excel spreadsheet containing the data in the report was supplied by the Study Director and used for these analyses. This included the units conversion of the amounts of active ingredient from mg into pounds and of the mass from µg to mg. The report data for inhalation exposure were unchanged other than the units conversions and some corrections to the tabulated air sampling durations in the original study report that were noted by the Study Director in September 2012. The hand wash dermal exposure data were used to develop exposure measurements for the following dermal exposure route:

- **Hands Only**. This case represents the dermal exposure to the hands only and is the mass from hand wash.

For two MEs (Reduced Splash ME 1 in 2012 and ME 8 in 2014, the hand exposure measurements were much higher than values for all other subjects. The liquid pour scenario is one in which unusually large hand exposures can occur through random dripping and spilling events that may be poorly associated with the total amount of active ingredient used. No adjustments were made in most of these analyses for these potential outliers. In Table 7 below, we analyze the impact of removing these outliers and show that the mean is reduced by about 30% and the 95th percentile is reduced by about 40%.

Inhalation exposure was measured using the air sampling OVS tubes. The inhalation exposure concentration (mg/m^3) was calculated by dividing the corrected residue mass by the volume of air drawn. The following inhalation exposure metrics are analyzed in this memorandum:

- **Inhalation Concentration (mg/m^3).** Concentration measured by the OVS tube.
- **Inhalation Dose (mg).** Inhalation Concentration (mg/m^3) × Air Sampling Duration (hr) × Breathing Rate for Light Activity (m^3/hr). A breathing rate of 1 m^3/hr is assumed.
- **8-Hour Time Weighted Average (TWA) Concentration (mg/m^3).** Average concentration over eight hours that includes this period of liquid pouring activity.
  Inhalation Concentration (mg/m^3) × Air Sampling Duration (hr) / 8 (hr).

Several of the measured residue values were below the level of quantitation (LOQ). Such values are called "non-detects." For most of the analyses in this memorandum, we replaced any residue value that was a non-detect by one half the LOQ. All the hand wash measurements in the study were above the LOQ. For the original 2012 study, all 6 of the OVS measurements in the Bottle scenario were below the LOQ of 10 ng. For the 2014 study, 2 of the 6 OVS measurements at a concentration of 0.2% were

below the LOQ of 1 ng. Also for the 2014 study, all 6 OVS measurements at a concentration of 0.02% were below the LOQ of 1 ng. Note that a measured residue value was also reported in the data set for the 8 OVS non-detects in the 2014 study, but those values were not used in the statistical analyses due to their unreliability. In Tables 8 and 14 below, we present the results of alternative analyses of values below the LOQ that demonstrate that because of the large number of inhalation exposure non-detects, the impact of the method for analyzing non-detect samples is large. Using the LOQ substitution instead of the half LOQ substitution increases the arithmetic mean and 95th percentile by about a factor of two, and using the censored data MLE method instead of the half LOQ substitution decreases the arithmetic mean and 95th percentile by about a factor of three. Using the censored data MLE method instead of the half LOQ substitution method increased the slope of the log exposure versus log pounds active ingredient handled from about 0.4 up to 1.0 or 1.3, with very wide confidence intervals.

In this memorandum we present the analysis of the unit or normalized exposure defined as the dermal (hands only) or inhalation exposure divided by the pounds of active ingredient handled. Estimates of the arithmetic and geometric means and standard deviation as well as the 95th percentile are computed using the empirical data as well as two statistical models: the lognormal simple random sampling model and the lognormal mixed model with a random study year effect. The empirical model calculates statistics for all 18 unit exposure measurements assuming the data are statistically independent. The lognormal simple random sampling model calculates statistics for all 18 unit exposure measurements, assuming the unit exposure measurements are statistically independent with a lognormal distribution. The lognormal mixed model assumes that the logarithm of the exposure has a normal distribution with the same mean for all MEs, a random study year effect, and a residual error. The random study year effect is a random value associated with each of the 18 workers that represents the possibility of clustering or association between the measurements in each of the two study years (2012 and 2014), expressing the possibility that changes over time in the study protocol, study personnel, or other temporal effects might cause differences in exposures to antimicrobials. Although one of the volunteers in the 2012 study poured liquids into trigger spray bottles from both the Conventional Pour and Reduced Splash containers, these analyses do not attempt to account for possible correlations between the two measurements on that one subject, treating this subject as if he or she was two different workers. There are insufficient data to distinguish this worker correlation from the other random effects in the statistical model.

For each summary statistic we present confidence intervals. We also compute the fold relative accuracy of the summary statistics and compare with the study design benchmark of 3-fold accuracy, which was generally met or almost met for the various arithmetic mean estimates but not the various 95th percentile estimates (using the parametric bootstrap). To evaluate the statistical models we present quantile-quantile plots of the data to determine whether the normalized exposure should be treated as being normally or lognormally distributed. We also present quantile-quantile plots of the residuals from the mixed model to evaluate the fitted models.

The statistical models for the normalized exposure assume that the mean value of the logarithm of the exposure is equal to an intercept plus the slope times the logarithm of the amount of active ingredient used, where the slope equals 1. To test this "log-log-linearity" assumption, the mixed model with a slope term was fitted to the data and a 95% confidence interval for the slope was calculated. A statistical test was used to determine if the slope was 1 or 0, corresponding either to a valid normalized exposure model or to a case where the exposure is independent of the amount of active ingredient used. We applied this test to the hands only exposure and to the three inhalation exposure metrics using the statistical mixed model. We also evaluated quadratic regression models.

The results for all the exposure routes show that the estimated intra-cluster correlation (ICC) coefficient for the study year effect is between 0.2 and 0.4, which implies that there are some study year effects, and therefore, differences between exposures for the two study years, treated as a random effect.

The linear mixed model results for the hands only exposure show a slope of 0.9. The statistical test does not reject log-log-linearity (slope equals one) at the 5% significance level. The statistical test rejects independence (slope equals zero) at the 5% significance level. For the inhalation exposure metrics using the half LOQ substitution method for the 14 (out of 18) non-detects, the estimated slopes are 0.4, log-log-linearity is rejected, and independence is rejected. However, using the preferred statistical approach of fitting a non-linear mixed model to the censored and non-censored data, the slope estimates were either 1.0 or 1.3 and the confidence intervals were either from −20 to +22 or from −29 to +32, so that the results were not at all significant.

Based on recommendations from the HSRB during the January, 2013 board meeting, the concentration of DDAC was varied in the 2014 supplemental study so that possible effects of concentration on exposure could be evaluated. In the 2014 supplemental study the DDAC concentration was 0.2% for six workers and 0.02% for the other six workers. In the original 2012 study the DDAC or ADBAC concentrations were 0.2% for all six workers. The analyses summarized above evaluated exposure as a function of the amount (mass) of active ingredient, which is the product of the volume poured (approximately a constant 40 fluid ounces for each worker in the Bottle scenario) and the concentration. Generally, the data showed that the exposures were about one tenth as large when the concentration was reduced by a factor of ten, indicating that the effects of concentration and mass are proportional. To statistically evaluate the possible incremental effects of concentration on exposure, a concentration fixed effect was added to the lognormal mixed model for the exposure per pound of active ingredient. For the hands only exposure, the concentration term was not statistically significant, indicating that the concentration value has no incremental effect on the normalized exposure. For the inhalation exposure, the concentration term was highly statistically significant, indicating that the concentration value has an incremental effect on the normalized exposure. However, these results for inhalation exposure should be regarded with caution because 14 of the 18 measurements (78%) of the inhalation data was below the LOQ, including all of the 2012 data (at 0.2% concentration) and all of the lower concentration (0.02%) 2014 data.

2. Summary Statistics of Exposure per Pound of Active Ingredient Handled

Tables 1 to 4 summarize the normalized exposure data (per lb active ingredient handled) with the summary statistics from the 18 measurements for each dermal and inhalation exposure route, for all 18 workers and for subsets of different years or concentrations. These analyses assume that the exposure measurements within each subset come from some unspecified distribution for that subset.

Table 1. Summary statistics for normalized hands only exposure (mg/lb AI) using empirical sampling model

Statistic	All	2012	2014	0.02%	0.2%
Arithmetic Mean	95	153	66	79	103
Arithmetic Standard Deviation	103	152	56	73	117
Geometric Mean	63	114	47	55	68
Geometric Standard Deviation	3	2	3	3	3
Min	8	38	8	11	8
5%	8	38	8	11	8
10%	11	38	11	11	26
25%	38	93	32	38	38
50%	74	105	58	60	85
75%	102	120	82	86	108

Statistic	All	2012	2014	0.02%	0.2%
90%	218	457	102	218	120
95%	457	457	218	218	457
Max	457	457	218	218	457

Table 2. Summary statistics for normalized inhalation concentration ((mg/m^3)/lb AI) using empirical sampling model

Statistic	All	2012	2014	0.02%	0.2%
Arithmetic Mean	0.0270	0.0347	0.0232	0.0358	0.0226
Arithmetic Standard Deviation	0.0133	0.0058	0.0145	0.0058	0.0140
Geometric Mean	0.0220	0.0343	0.0176	0.0354	0.0173
Geometric Standard Deviation	2.1681	1.1858	2.3793	1.1774	2.3470
Min	0.0040	0.0262	0.0040	0.0281	0.0040
5%	0.0040	0.0262	0.0040	0.0281	0.0040
10%	0.0040	0.0262	0.0040	0.0281	0.0040
25%	0.0123	0.0322	0.0099	0.0320	0.0099
50%	0.0321	0.0337	0.0256	0.0348	0.0246
75%	0.0359	0.0399	0.0348	0.0411	0.0337
90%	0.0423	0.0423	0.0411	0.0438	0.0399
95%	0.0438	0.0423	0.0438	0.0438	0.0423
Max	0.0438	0.0423	0.0438	0.0438	0.0423

Table 3. Summary statistics for normalized inhalation dose (mg/lb AI) using empirical sampling model

Statistic	All	2012	2014	0.02%	0.2%
Arithmetic Mean	0.0064	0.0093	0.0049	0.0075	0.0058
Arithmetic Standard Deviation	0.0032	0.0009	0.0029	0.0006	0.0038
Geometric Mean	0.0052	0.0092	0.0039	0.0075	0.0043
Geometric Standard Deviation	2.2211	1.1045	2.3123	1.0919	2.5403
Min	0.0008	0.0080	0.0008	0.0066	0.0008
5%	0.0008	0.0080	0.0008	0.0066	0.0008
10%	0.0009	0.0080	0.0009	0.0066	0.0009
25%	0.0031	0.0086	0.0023	0.0069	0.0023
50%	0.0075	0.0093	0.0058	0.0075	0.0065
75%	0.0086	0.0096	0.0075	0.0080	0.0093
90%	0.0096	0.0107	0.0080	0.0082	0.0096

Statistic	All	2012	2014	0.02%	0.2%
95%	0.0107	0.0107	0.0082	0.0082	0.0107
Max	0.0107	0.0107	0.0082	0.0082	0.0107

Table 4. Summary statistics for normalized inhalation 8-hour time weighted average concentration ((mg/m^3)/lb AI) using empirical sampling model

Statistic	All	2012	2014	0.02%	0.2%
Arithmetic Mean	0.0008	0.0012	0.0006	0.0009	0.0007
Arithmetic Standard Deviation	0.0004	0.0001	0.0004	0.0001	0.0005
Geometric Mean	0.0006	0.0012	0.0005	0.0009	0.0005
Geometric Standard Deviation	2.2211	1.1045	2.3123	1.0919	2.5403
Min	0.0001	0.0010	0.0001	0.0008	0.0001
5%	0.0001	0.0010	0.0001	0.0008	0.0001
10%	0.0001	0.0010	0.0001	0.0008	0.0001
25%	0.0004	0.0011	0.0003	0.0009	0.0003
50%	0.0009	0.0012	0.0007	0.0009	0.0008
75%	0.0011	0.0012	0.0009	0.0010	0.0012
90%	0.0012	0.0013	0.0010	0.0010	0.0012
95%	0.0013	0.0013	0.0010	0.0010	0.0013
Max	0.0013	0.0013	0.0010	0.0010	0.0013

The summary statistics in Table 1 show that the normalized hands only exposure was about twice as high in 2012 compared to 2014 and about 25% higher for the 0.2% concentration versus the 0.02% concentration of the active ingredient. Since the study in 2012 only used the chemical at a 0.2% concentration, it is not easy to distinguish the effects of the study year and concentration on the normalized exposure.

The summary statistics in Tables 2 to 4 show that the normalized inhalation exposure was about 50% to 100% higher in 2012 compared to 2014 and up to about 50% higher for the 0.02% concentration versus the 0.2% concentration of the active ingredient. Since the study in 2012 only used the chemical at a 0.2% concentration, and since 14 of the 18 inhalation measurements were below the LOQ and estimated as half the LOQ, it is not easy to distinguish the effects of the study year and concentration on the normalized exposure.

3. Statistical Models

The statistical analyses of the normalized exposure use the following three alternative statistical models. Let X be the normalized exposure and X = exp(Y) so that Y = log (X), where log denotes the natural logarithm. LnGM is the log of the geometric mean. Let Z95 be the 95th percentile of a standard normal distribution, approximately 1.645.

- Empirical simple random sampling model. Code “s.” Assumes that all the values of X were randomly drawn from an unspecified distribution. Ignores within-study-year correlations. Gives empirical estimates such as in Tables 1 to 4 above.

- Y = LnGM + Error. Error is independent and identically distributed with mean 0 and the same variance for every measurement.
- AMs = Arithmetic mean of X values
- GMs = Geometric mean of X values = exp(LnGM) (= GMu)
- GSDs = Geometric standard deviation of X values (= GSDu)
- P95s = 95th percentile of X values

- Lognormal simple random sampling model. Code "u." Assumes that all the values of X were randomly drawn from a lognormal distribution. Ignores within-study-year correlations.
  - Y = LnGM + Error. Error is normally distributed with mean 0, variance Vu, and standard deviation Su = √Vu.
  - AMu = Modeled arithmetic mean of X values = exp(LnGM) exp(½ Vu)
  - GMu = Modeled geometric mean of X values = exp(LnGM)
  - GSDu = Modeled geometric standard deviation of X values = exp(Su)
  - P95u = Modeled 95th percentile of X values = exp(LnGM) exp(Z95×Su)

- Lognormal mixed model. Code "m." Assumes that the 2 study year random effects were independently randomly drawn from a normal distribution and that the 18 random error terms were independently drawn from another normal distribution. The error term for each worker and exposure measurement is the sum of the study year effect for that worker and the within-worker random error term.
  - Y = LnGM + Year + Error. Year is normally distributed with mean 0, variance Vy, and standard deviation Sy= √Vy Error is normally distributed with mean 0, variance Vr, and standard deviation Sr = √Vr. Define V = Vy+ Vr and S = √V. V is the variance of Y, and S is the standard deviation of Y.
  - ICC = Intra-study-year coefficient = Vy/V.
  - AMm = Modeled arithmetic mean of X values = exp(LnGM) exp(½ V).
  - GMm = Modeled geometric mean of X values = exp(LnGM).
  - GSDm = Modeled geometric standard deviation of X values = exp(S).
  - P95m = Modeled 95th percentile of X values = exp(LnGM) exp(Z95×S).

For the lognormal mixed model, the ICC value estimates the clustering effect of multiple measurements in the same study year and lies between 0 (no clustering) and 1 (complete clustering and negligible within-cluster variation). An ICC of 0 is when measurements in the same study year are uncorrelated. An ICC of 1 is when for each study year all the exposure measurements are identical. This ICC is analogous to the ICC defined for the mop, wipe, and aerosol that accounted for the possible effects of different study locations. In this case the physical location was the same for the original and supplemental studies, but there may have been other random effects due to changes in personnel, environmental effects, and study features (e.g., dosimeters were not worn in the supplemental study, and the 24 fl oz Conventional Pour container in the main study was replaced by a 16 fl oz Conventional Pour container in the supplemental study).

Table 5 presents the arithmetic mean and 95th percentile estimates from the lognormal mixed model, together with 95% confidence intervals, for all the exposure routes. These are the values of AMm and P95m. The other summary statistics are presented in more detail below.

Table 5. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure

Exposure Route	Clothing	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
Dermal (mg/lb AI)	Hands only	120.4 (45.7, 379.0)	386.6 (124.1, 1382.1)
Inhalation Concentration (mg/m^3/lb AI)		0.0334 (0.0164, 0.0733)	0.0924 (0.0388, 0.2400)
Inhalation Dose (mg/lb AI)		0.0087 (0.0034, 0.0268)	0.0255 (0.0081, 0.0957)
Inhalation 8-hr TWA (mg/m^3/lb AI)		0.0011 (0.0004, 0.0033)	0.0032 (0.0010, 0.0120)

For each exposure route, the above three statistical models were fitted to the observed data and the summary statistics listed above were calculated together with 95% confidence intervals. The 95% confidence intervals in Table 5 were computed using a parametric bootstrap. For these calculations, the parametric bootstrap simulations were all generated from the fitted lognormal mixed model, even for the empirical and simple random sample summary statistics, on the basis that the mixed model is the best choice for modeling the data, even if the summary statistics are developed from a simpler statistical model. For example, in the "All" columns from Tables 1 to 4, the empirical arithmetic means are presented, which are the arithmetic means of the 18 measurements. To estimate the uncertainty of those empirical arithmetic means, data are simulated from the lognormal mixed model to calculate the parametric bootstrap confidence intervals. The arithmetic means in Table 5 are estimated using the lognormal mixed model, which is also used to estimate the confidence intervals in Table 5. The unit exposure estimates (from the lognormal mixed model) displayed in Table 5 are recommended over the empirical arithmetic means and 95th percentiles displayed in Tables 1 to 4.

The algorithm used was as follows:

Step 1:
Simulate 18 random variables Y, X from the estimated lognormal distribution superimposed upon the observed sampling structure ---;

Z = RanNor (Seed) ×Sy (2 values, one for each study year)

Y = Z + LnGM + RanNor(Seed)×Sr

X = exp(Y)

where:

LnGM = intercept of mixed effect log-log regression model

Sy = square root of between study year variance

Sr = square root of within worker variance under mixed-effect model

The allocation of each worker to the two study years is exactly the same as the observed random design configuration, with six workers in 2012 and twelve workers in 2014.

Step 2:
For Y:

Calculate GMs = exp(EAM)

Calculate GSDs = exp(Su)

Calculate AMu = GMs×exp(0.5×Su×Su)

Calculate P95u = GMs× exp(Z95×Su)

Fit mixed lognormal model to simulated Y values

Under mixed-effects model:

Calculate GMm = exp(intercept of mixed-effects model)

Calculate GSDm = exp(square root (total variance V under mixed-effects model))

Calculate ICC = Vy /V

Calculate AMm = exp(intercept + 0.5×V)

Calculate P95m = exp(intercept + Z95×S)

where:

EAM = sample arithmetic mean of Y = AMu

Su = standard deviation of Y

V = total variance under mixed-effects model

S = square root of V

Vy = between study year variance

For X:

Calculate arithmetic mean AMs

Calculate 95th percentile P95s

Step 3: Repeat Steps 1 and 2 10,000 times.

Steps 1 to 3 result in 10,000 values each for each of GSDs, GMs, GMm, AMs, AMm, AMu, P95s, P95m, P95u, GSDm and ICC. 95% confidence intervals can be defined for each parameter by the 2.5th and 97.5th percentiles (lower and upper, respectively) of the bootstrap distribution of that corresponding parameter. Note that by definition, GSDs = GSDu and GMs = GMu.

4. Comparison with Previous Analyses

Of interest is whether the normalized exposure arithmetic mean and 95th percentile estimates from the combined analysis of 18 Bottle scenario MEs are different from the estimates calculated from the original analyses of the Liquid Pour Study that included only six Bottle scenario MEs. Those analyses also used data from the Conventional Pour and Reduced Splash scenarios (fifteen MEs each). In Table 6, the results from Table 5 above are compared with the corresponding estimates from the original analysis, either on the assumption that the variances were the same for all three groups (Bottle, Conventional Pour, Reduced Splash), or the alternative assumption that the variances could differ between groups. For the original study, we also present the estimates for the Long Dermal clothing scenario representing workers wearing long pants and long-sleeved shirts. Since dosimeters were not worn for the supplemental study, Long Dermal estimates are not available for the combined study. The results in Table 6 use all the data and all non-detects are replaced by half the LOQ.

Table 6. Arithmetic mean and 95th percentile estimates from the lognormal mixed model for normalized exposure, comparing the original study and combined study for the Bottle scenario

Exposure Route	Clothing	Study	Equal group variances?	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
Dermal (mg/lb AI)	Hands only	Combined	N/A	120.4 (45.7, 379.0)	386.6 (124.1, 1382.1)
		Original	Yes	314.0 (89.8, 1115.2)	1178.7 (315.2, 4245.5)
			No	159.2 (76.5, 368.8)	427.7 (147.7, 1228.0)
Long Dermal (mg/lb AI)	Long pants and long shirt	Original	Yes	298.5 (89.9, 1005.7)	1105.5 (309.4, 3817.5)
			No	160.5 (78.5, 360.6)	425.7 (150.3, 1184.0)
Inhalation Concentration (mg/m^3/lb AI)		Combined	N/A	0.0334 (0.0164, 0.0733)	0.0924 (0.0388, 0.2400)
		Original	Yes	0.0473 (0.0240, 0.0930)	0.1283 (0.0613, 0.2640)
			No	0.0348 (0.0302, 0.0405)	0.0453 (0.0365, 0.0595)
Inhalation Dose (mg/lb AI)		Combined	N/A	0.0087 (0.0034, 0.0268)	0.0255 (0.0081, 0.0957)
		Original	Yes	0.0125 (0.0065, 0.0240)	0.0331 (0.0162, 0.0664)
			No	0.0092 (0.0084, 0.0102)	0.0109 (0.0094, 0.0129)
Inhalation 8-hr TWA (mg/m^3/lb AI)		Combined	N/A	0.0011 (0.0004, 0.0033)	0.0032 (0.0010, 0.0120)
		Original	Yes	0.0016 (0.0008, 0.0030)	0.0041 (0.0020, 0.0083)
			No	0.0011 (0.0010, 0.0013)	0.0014 (0.0012, 0.0016)

The Table 6 comparison shows that the combined study arithmetic mean normalized exposures are similar to, but lower than, the estimates from the original study not assuming equal variances. The combined study 95th percentile normalized exposures are more similar to the estimates from the original study assuming equal variances, except for the hands only exposures. The confidence intervals for the combined study are approximately as wide as those from the original study. Although the combined study has three times as many MEs for the Bottle scenario (18 instead of 6), the statistical analysis of the original Liquid Pour study used data from 36 MEs (for all three groups) and some of the information in the data from the 30 Conventional Pour and Reduced Splash MEs was used in the statistical models to develop the original statistical estimates for the Bottle scenario.

5. Outliers and Non-detects

For all the analyses presented in this memorandum, except for Tables 7, 8 and 14 (see below for discussion on Table 14), all the data values were used and values below the LOQ were replaced by one half of the LOQ.

Outliers

For two MEs (Reduced Splash ME 1 in group 1a from the 2012 study and ME 8 at concentration 0.02%), the hands only exposure measurements were much higher when normalized by the amount of active ingredient than values for the other subjects (about two or four times higher than the third highest unit exposure). The liquid pour scenario is one in which unusually large hand exposures can occur through random dripping and spilling events that may be poorly associated with the total amount of active ingredient used. To investigate the impact of these potential outliers, we recomputed the arithmetic mean and 95th percentile estimates (and parametric bootstrap confidence intervals) for Hands Only exposure after excluding the dermal data for these measurements. As shown in Table 7, the mean is reduced by 31% and the 95th percentile is reduced by 39%. The outliers have a substantial effect.

Table 7. Hand Only Dermal summary statistics calculated with and without the potential outlier data for Reduced Splash ME 1 in group 1a in 2012 and ME8 in 2014

Data	Arithmetic mean (mg / lb AI)	95th percentile (mg / lb AI)
All 18 values	120.4 (45.7, 379.0)	386.6 (124.1, 1382.1)
Exclude 2 outliers	82.6 (37.8, 198.5)	234.5 (91.9, 671.2)

Non-detects

In Table 8 we investigated the impact of the inhalation exposure values below the LOQ, i.e., censored values. All the hand wash measurements in the study were above the LOQ. For the 2012 study year, all 6 OVS measurements of the 6 Bottle MEs were below the LOQ. For the 2014 study year, all 6 OVS measurements of the 6 Bottle MEs at a concentration of 0.02% were below the LOQ and 2 of the 6 OVS measurements of the 6 Bottle MEs at a concentration of 0.2% were below the LOQ. For all three inhalation exposure metrics, we computed the arithmetic mean and 95th percentiles using the recommended substitution of one half the LOQ for values below the LOQ and compared those results to estimates using the alternative substitution of the LOQ (the maximum possible exposure estimate); substitution of zero for inhalation exposure is not useful because the statistical models use the logarithms of the exposure which cannot be calculated when the minimum exposure is zero. We also investigated a censored maximum likelihood statistical method described in the following paragraphs.

The mixed model fitted to the unit exposures from the censored and uncensored liquid pour exposure data has the form:

Log (Exposure/Pounds of Active Ingredient) = Intercept + Year + Error.

In this model, Year is a normally distributed random effect variable with independent, identically distributed values for each study year, and Error is a normally distributed error variable with independent, identically distributed values for each total exposure measurement. This model was fitted using the SAS procedure NLMIXED, using code adapted from the article “Analysis of Lognormally Distributed Exposure Data with Repeated Measures and Values below the Limit of Detection Using SAS” (YAN JIN, MISTY J. HEIN, JAMES A. DEDDENS and CYNTHIA J. HINES, Ann Occup Hyg (2011) 55(1): 97-112, doi:10.1093/annhyg/meq061). For these calculations, the marginal likelihood averaged over the random effects is maximized. The fitted model has values for the following parameters: the intercept, Variance of Year, Variance of Error. These parameters are abbreviated as intercept, varyear, and varerror. The corresponding mixed model parameters V, S, GSDm, AMm, GMm, P95m and ICC are then calculated as

GMm = exp(intercept),

V = total variance = varyear + varerror

ICC = varyear/V

S = √V

GSDm = exp(S)

AMm = GMm × exp(V/2)

Z95 = 95th percentile of a standard normal distribution

P95m = GMm × exp(Z95 × S)

Separate models were fitted for each inhalation scenario.

These are the estimates of the mixed model parameters calculated from the combination of the censored and uncensored data. To calculate confidence intervals for these mixed model parameters, a parametric bootstrap method was used. This is exactly the same bootstrap method that was used for the original case where the non-detects were replaced by half the LOQ. 10,000 values of the unit exposure were simulated from this mixed model, and for each simulation, the mixed model was fitted to the simulated data using the MIXED procedure. The simulated unit exposures are all uncensored numerical values even though the corresponding residues can be lower than the LOQs. The confidence intervals for each parameter range from the 2.5th percentile to the 97.5th percentile.

Results for the inhalation concentration, inhalation dose, and time-weighted 8-hour average inhalation concentration are presented in Table 8. The results are compared for the default substitution of half the LOQ, the alternative substitution of the LOQ, and estimates calculated using the maximum likelihood method for censored data, referred to as "Censored data MLE."

Table 8. Inhalation exposure summary statistics calculated using alternative estimated exposures for values below the LOQ

Exposure metric	Units	Method for substituting values below the LOQ	Arithmetic mean	95th percentile
Inhalation concentration	mg/m^3/lb AI	Substitute ½ LOQ	0.0334 (0.0164, 0.0733)	0.0924 (0.0388, 0.2400)
		Substitute LOQ	0.0707 (0.0263, 0.2301)	0.2240 (0.0701, 0.8362)
		Censored data MLE	0.0112 (0.0088, 0.0145)	0.0223 (0.0158, 0.0327)
Inhalation dose	mg/m^3/lb AI	Substitute ½ LOQ	0.0087 (0.0034, 0.0268)	0.0255 (0.0081, 0.0957)
		Substitute LOQ	0.0187 (0.0054, 0.0929)	0.0618 (0.0143, 0.3353)
		Censored data MLE	0.0026 (0.0020, 0.0033)	0.0052 (0.0036, 0.0077)
Inhalation 8-hour time weighted average	mg/m^3/lb AI	Substitute ½ LOQ	0.0011 (0.0004, 0.0033)	0.0032 (0.0010, 0.0120)
		Substitute LOQ	0.0023 (0.0007, 0.0116)	0.0077 (0.0018, 0.0419)

Exposure metric	Units	Method for substituting values below the LOQ	Arithmetic mean	95th percentile
		Censored data MLE	0.0003 (0.0002, 0.0004)	0.0007 (0.0005, 0.0010)

The results in Table 8 demonstrate very large impacts of the alternative approaches for treating values below the LOQ on the inhalation exposure metrics, because of the large percentage of OVS values below the LOQ: Using the LOQ substitution instead of the half LOQ substitution increases the arithmetic mean and 95th percentile by about a factor of two, and using the censored data MLE method instead of the half LOQ substitution decreases the arithmetic mean and 95th percentile by about a factor of three. Although the true values of the non-detect measurements are unknown, these results show strong evidence that the half LOQ substitution method strongly overestimates the exposure concentrations, especially for the 2012 study that had high LOQ values.

6. Fold Relative Accuracy

Fold relative accuracy (*fRA*) is a measure that can be used to determine how well a statistic can describe its population parameter. Let us assume θ is a parameter and T is the sample statistic of θ (i.e., an estimate of θ). If the 2.5th and 97.5th percentiles of the sampling distribution of T can be denoted by $T_{2.5}$ and $T_{97.5}$, respectively, then the 95th percentile of sample fold relative accuracy can be theoretically calculated using the following formula provided in the AHETF Governing Document (AHETF, 2007, pg. 136 and AHETF, 2011, pg. 120):

$$fRA_{95} = \text{Max}\,(T_{97.5} / \theta, \theta / T_{2.5})$$

The actual value of θ is unknown. Thus, fRA_{95} was calculated by substituting θ with T. If the fRA_{95} of a statistic were equal to 3, then it would be correct to say: "At least 95% of the time the sample statistic will be accurate to within 3-fold of the population value". According to the AHETF Governing Document, the statistical design of the exposure monitoring study should be adequate to produce a fRA_{95} less than or equal to 3. Thus the confidence intervals calculated in the above algorithm can be used to estimate the fold relative accuracy and compare the observed fRA with the study design benchmark of 3. If the observed fold relative accuracy is greater than 3, this means that the experiment did not meet the benchmark, which would be due to differences between the distributions of the CMA data used to design the study and the experimental data collected in the study. If the fold relative accuracy benchmark is not met, then it might be desirable to collect more data for this scenario in order to meet the benchmark. Fold relative accuracy was not computed for the ICC since the estimated ICC or its lower bound is 0 in many cases.

Following HSRB recommendations, confidence intervals were estimated using both a parametric bootstrap approach, as described above, and the following non-parametric bootstrap approach. The non-parametric bootstrap method should be more robust since it does not assume that the fitted parametric model is the correct one. For the non-parametric bootstrap, exactly the same algorithm was used except that Step 1 above was replaced by the following:

Step 1:
Simulate 18 random variables Y, X by resampling at random with replacement from the original data:

For Study year j, the original exposure data are X(1), X(2), …, X(n_j), where n_j is the number of workers in study year j (n_{2012} equals 6 and n_{2014} equals 12).

Sample n_j values at random with replacement from the exposure values X(1), X(2), …, X(n_j). This gives the n_j simulated random variables X from year j.

Repeat for both years (j = 2012 and 2014).

Y = log(X).

The Y, X values were independently resampled from the two study years in order to preserve the covariance structure.

7. Detailed Summary Statistics with Confidence Intervals and Fold Relative Accuracy

Tables 9 to 12 present the estimates, parametric and non-parametric confidence intervals and fold relative accuracy values for all the summary statistics for the one dermal and three inhalation exposure routes, respectively.

Table 9. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized hands only exposure (mg/lb AI)

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.6	1.9	3.8	1.5	1.7	3.5	1.5
GSDm	2.8	1.9	5.1	1.8	1.8	4.3	1.6
ICC	0.3	0.0	0.7		0.0	0.7	
GMs	63.3	28.8	172.3	2.7	42.9	92.3	1.5
GMm	70.6	29.4	167.0	2.4	48.5	105.0	1.5
AMs	95.1	42.4	283.6	3.0	59.5	141.9	1.6
AMu	100.1	43.7	301.2	3.0	64.2	155.8	1.6
AMm	120.4	45.7	379.0	3.1	71.0	252.7	2.1
P95s	456.9	123.1	1571.6	3.7	113.3	456.9	4.0
P95u	305.6	117.8	1017.9	3.3	155.6	530.8	2.0
P95m	386.6	124.1	1382.1	3.6	169.5	951.0	2.5

Table 10. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation concentration (mg/m^3/lb AI)

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.1681	1.6568	2.9033	1.3	1.5422	2.6454	1.4
GSDm	2.2827	1.6770	3.5738	1.6	1.5523	3.0342	1.5
ICC	0.2284	0.0000	0.7130		0.0000	0.5525	
GMs	0.0220	0.0121	0.0467	2.1	0.0158	0.0296	1.4
GMm	0.0238	0.0123	0.0454	1.9	0.0186	0.0301	1.3
AMs	0.0270	0.0156	0.0647	2.4	0.0216	0.0324	1.3
AMu	0.0297	0.0159	0.0664	2.2	0.0234	0.0347	1.3
AMm	0.0334	0.0164	0.0733	2.2	0.0291	0.0383	1.1
P95s	0.0438	0.0386	0.2811	6.4	0.0399	0.0438	1.1
P95u	0.0785	0.0375	0.1946	2.5	0.0558	0.0955	1.4

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
P95m	0.0924	0.0388	0.2400	2.6	0.0595	0.1240	1.6

Table 11. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation dose (mg/lb AI)

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.2211	1.6502	3.2848	1.5	1.5357	2.7757	1.4
GSDm	2.4546	1.6663	4.6723	1.9	1.6159	3.3514	1.5
ICC	0.3970	0.0000	0.8234		0.2191	0.6466	
GMs	0.0052	0.0024	0.0141	2.7	0.0037	0.0069	1.4
GMm	0.0058	0.0024		2.4	0.0046	0.0073	1.3
AMs	0.0064	0.0032		3.2	0.0053	0.0074	1.2
AMu	0.0071	0.0032	0.0213	3.0	0.0059	0.0080	1.2
AMm	0.0087	0.0034	0.0268	3.1	0.0077	0.0100	1.1
P95s	0.0107	0.0081	0.0848	7.9	0.0094	0.0107	1.1
P95u	0.0191	0.0076	0.0643	3.4	0.0133	0.0229	1.4
P95m	0.0255	0.0081	0.0957	3.8	0.0157	0.0346	1.6

Table 12. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation 8-hour time-weighted average (mg/m^3/lb AI)

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.2211	1.6502	3.2848	1.5	1.5357	2.7757	1.4
GSDm	2.4546	1.6663	4.6723	1.9	1.6159	3.3514	1.5
ICC	0.3970	0.0000	0.8234		0.2191	0.6466	
GMs	0.0006	0.0003	0.0018	2.7	0.0005	0.0009	1.4
GMm	0.0007	0.0003	0.0017	2.4	0.0006	0.0009	1.3
AMs	0.0008	0.0004	0.0025	3.2	0.0007	0.0009	1.2
AMu	0.0009	0.0004	0.0027	3.0	0.0007	0.0010	1.2
AMm	0.0011	0.0004	0.0033	3.1	0.0010	0.0013	1.1
P95s	0.0013	0.0010	0.0106	7.9	0.0012	0.0013	1.1
P95u	0.0024	0.0009	0.0080	3.4	0.0017	0.0029	1.4
P95m	0.0032	0.0010	0.0120	3.8	0.0020	0.0043	1.6

Tables 9 to 12 show that the ICC estimated value is between 0.2 and 0.4 for the hands only dermal and all three inhalation exposure metrics showing that there is some variation between the two study years and some correlation between measurements in the same study year.

Tables 9 to 12 also show that the study benchmark design value of 3 for the fold relative accuracy was generally met or almost met for the summary statistics other than the various 95th percentile estimates. For the parametric bootstrap, the benchmark was not met for: hands only AMm (fRA = 3.1), P95s, P95u, and P95m; inhalation concentration P95s; inhalation dose and time-weighted average AMs (fRA = 3.2), AMm (fRA = 3.1), P95s, P95u, and P95m. For the non-parametric bootstrap, the benchmark was met in all cases except for P95s for hands only. For the inhalation exposure metrics, the non-parametric bootstrap confidence intervals may not very reliable because of the large number of non-detects that are substituted by half the LOQ, leading to much narrower uncertainty intervals then the parametric bootstrap, for which the simulated exposure values can be any non-negative value.

8. Empirical Quantile Plots

Quantile-quantile plots of the normalized exposure values were used to evaluate whether the data were lognormally distributed, as implied by the assumed statistical mixed models. These plots were intended to help determine whether the data supported using untransformed normalized exposure values (exposure per pound AI) or log-transformed values or neither. The plots are not intended to evaluate the fitted statistical models, for which the residual quantile plots, described in the next subsection, were developed.

In each case the quantile-quantile plot compared the observed quantiles of the 18 measured values with the corresponding quantiles of a normal or lognormal distribution. For convenience, the corresponding arithmetic mean normalized exposure was subtracted from the normalized exposure when creating the normal distribution plots, and the corresponding arithmetic mean logarithm of the normalized exposure was subtracted from the logarithm of the normalized exposure when creating the lognormal distribution plots. This subtraction simply rescales the y-axes without affecting the interpretation of the plot. (For the original liquid pour study, we subtracted different means for each group, but this does not apply for these Bottle only analyses.) A perfect fit would imply that the plotted values lie in a straight line. The quantile-quantile plots for the hands only and inhalation concentration exposure are presented in Figures 1 to 4. For the hands only exposure, the plots clearly show that the lognormal distribution is a better fit than a normal distribution, and that the lognormal distribution fits reasonably well. For the inhalation concentration, the plots show a preference for the normal distribution, which is likely because of the large numbers of non-detects; most of the mg exposure values are replaced by half the applicable LOQ, and the air flow rates, volumes poured, and AI are approximately equal across all the MEs for a concentration percentage. The quantile plots for the inhalation dose and time-weighted average (not shown) look similar to the plots for the inhalation concentration.

Quantile plot normalized hands only exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled

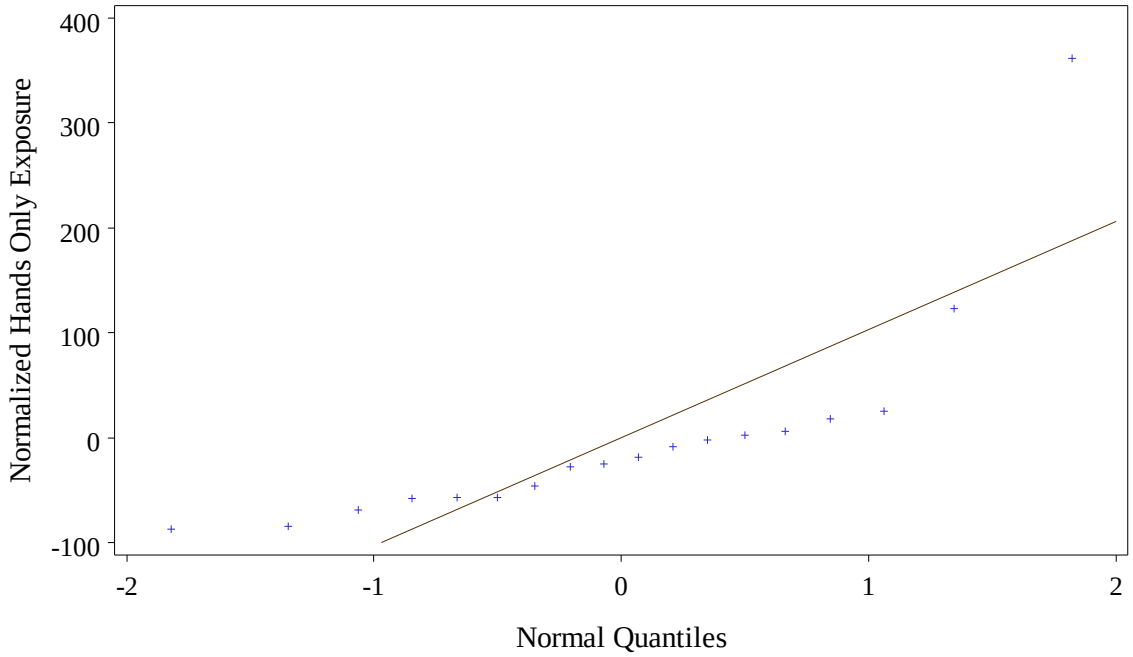

Figure 1. Empirical quantile plot for hands only with a normal distribution

Quantile plot normalized hands only exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled

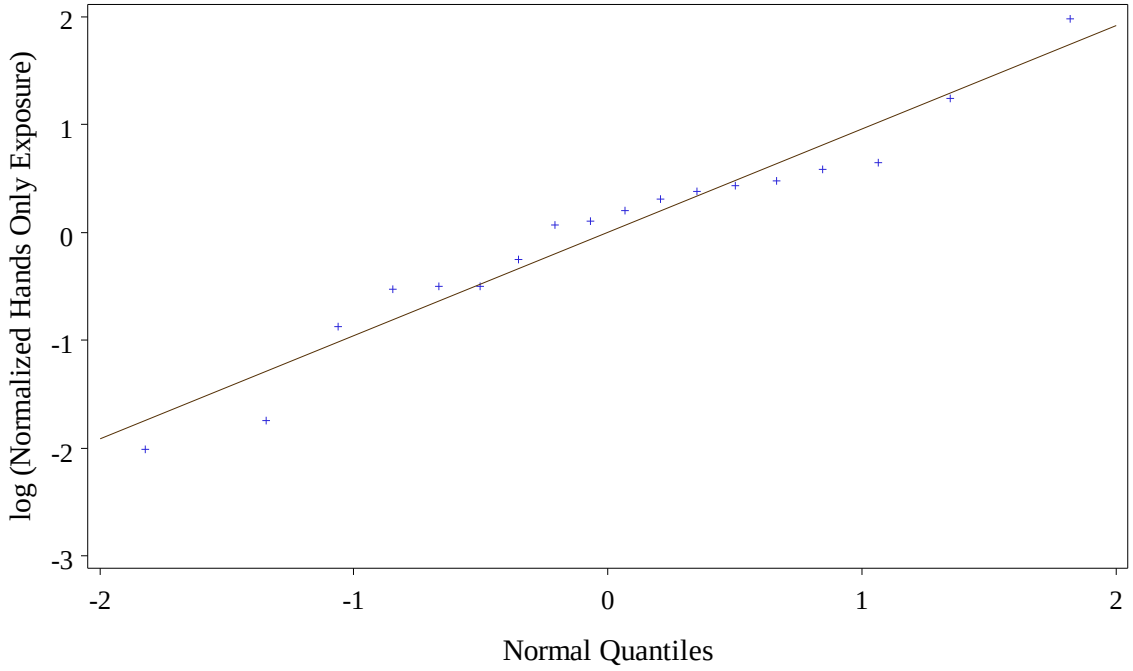

Figure 2. Empirical quantile plot for hands only with a lognormal distribution

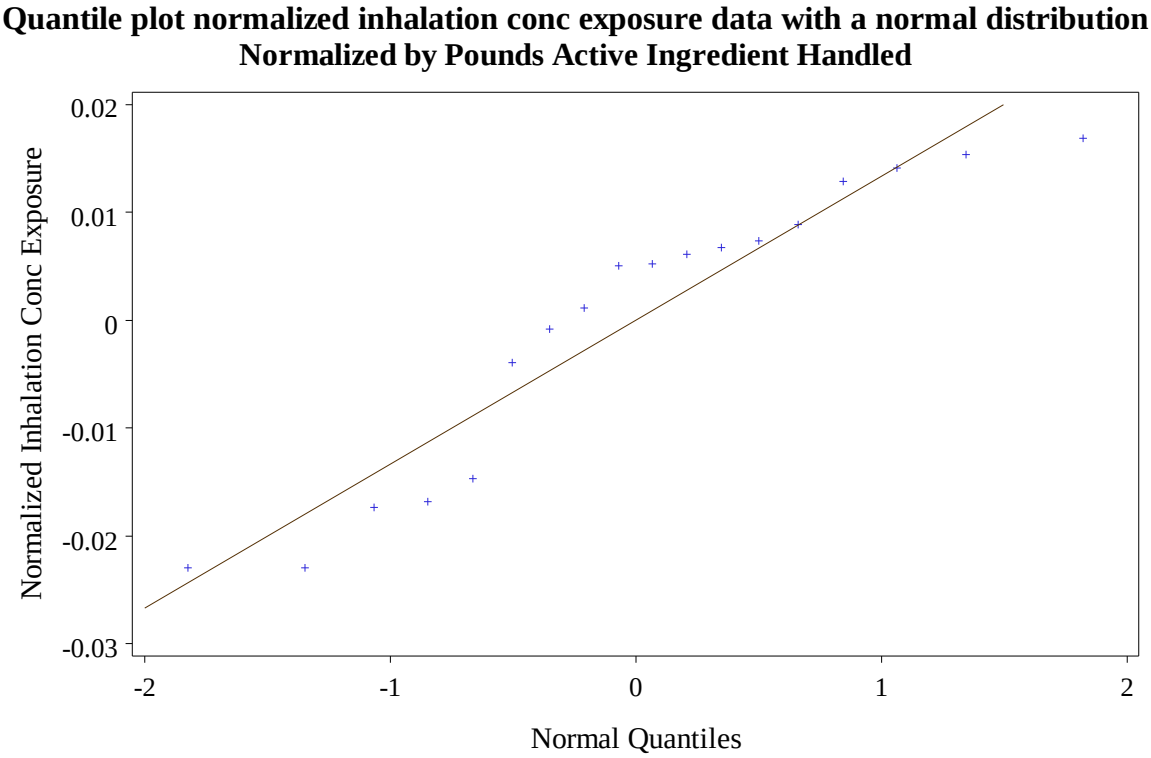

Figure 3. Empirical quantile plot for inhalation concentration with a normal distribution

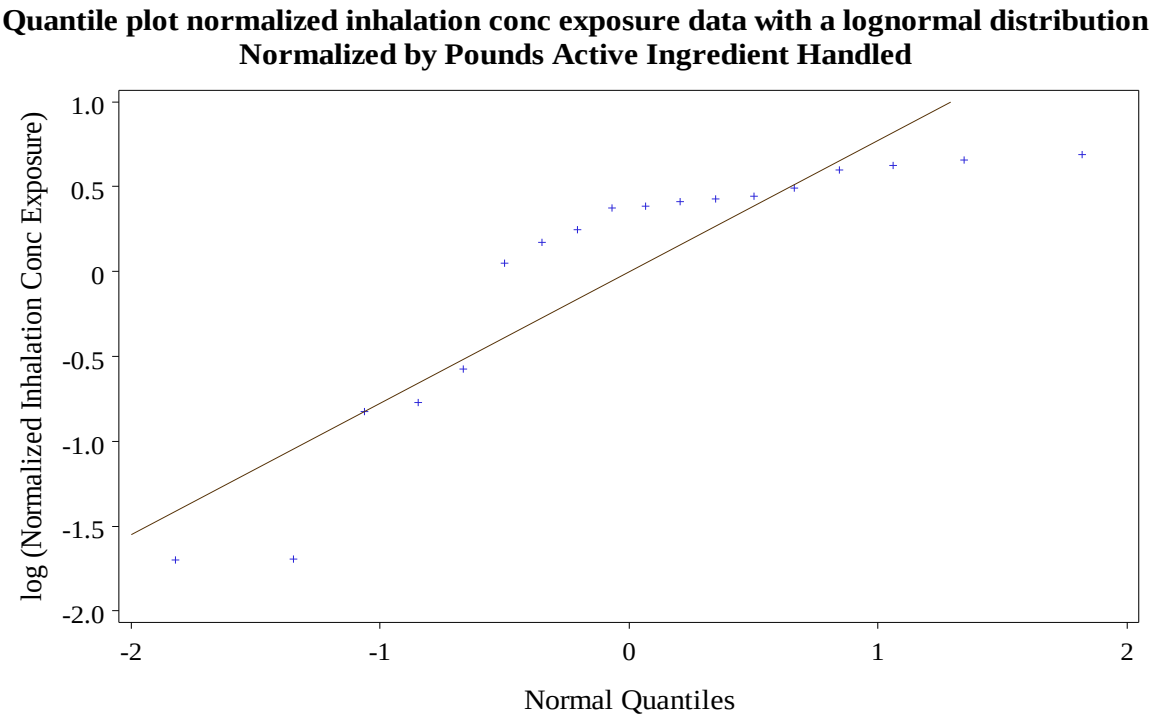

Figure 4. Empirical quantile plot for inhalation concentration with a lognormal distribution

9. Residual Quantile Plots

Quantile-quantile plots of the studentized residuals from the lognormal mixed model were used to evaluate the performance and goodness-of-fit of the fitted models. The studentized residual is calculated as the marginal residual divided by an estimate of

the standard deviation of the marginal residual. The marginal residual is defined as the natural logarithm of the normalized exposure minus the predicted value (which in this case is the intercept of the fitted model). The studentized residuals each have a variance of 1. The tendency of the points to lie along a straight line supports the use of that statistical model. The quantile-quantile plots of the studentized residuals for the hands only, inhalation concentration, inhalation dose, and inhalation time-weighted average exposure are presented in Figures 5 to 8, respectively.

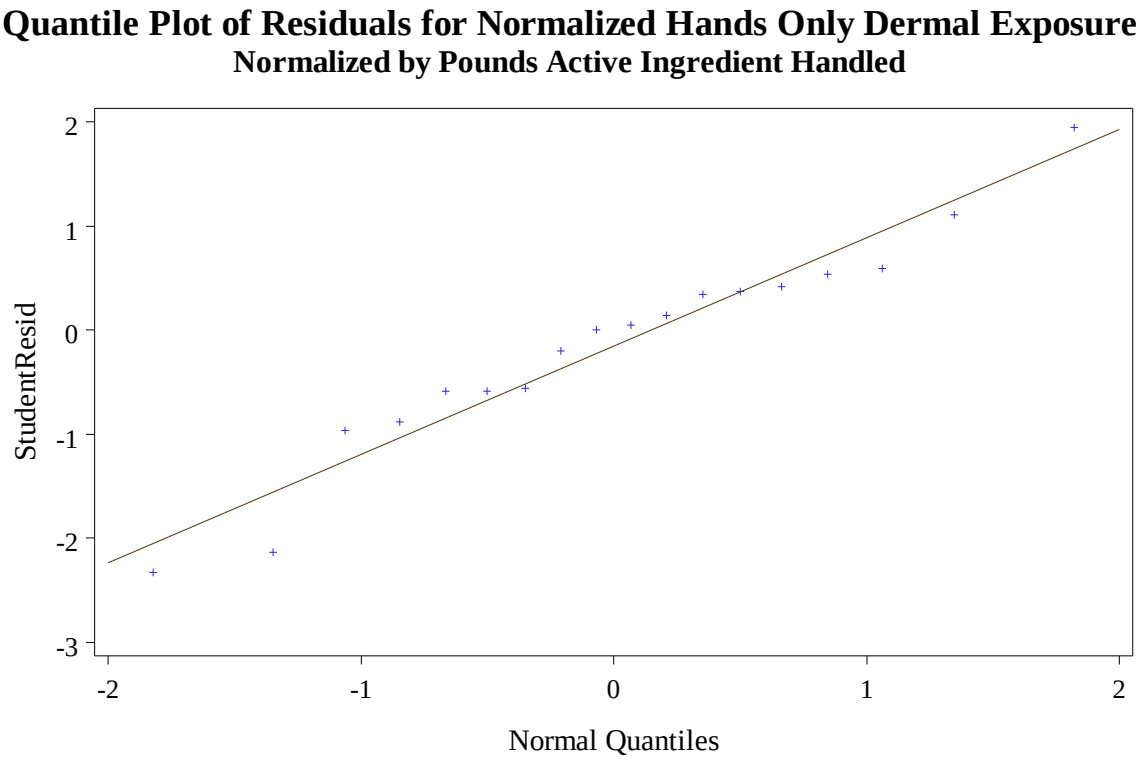

Figure 5. Quantile plot of studentized residuals for hands only exposure

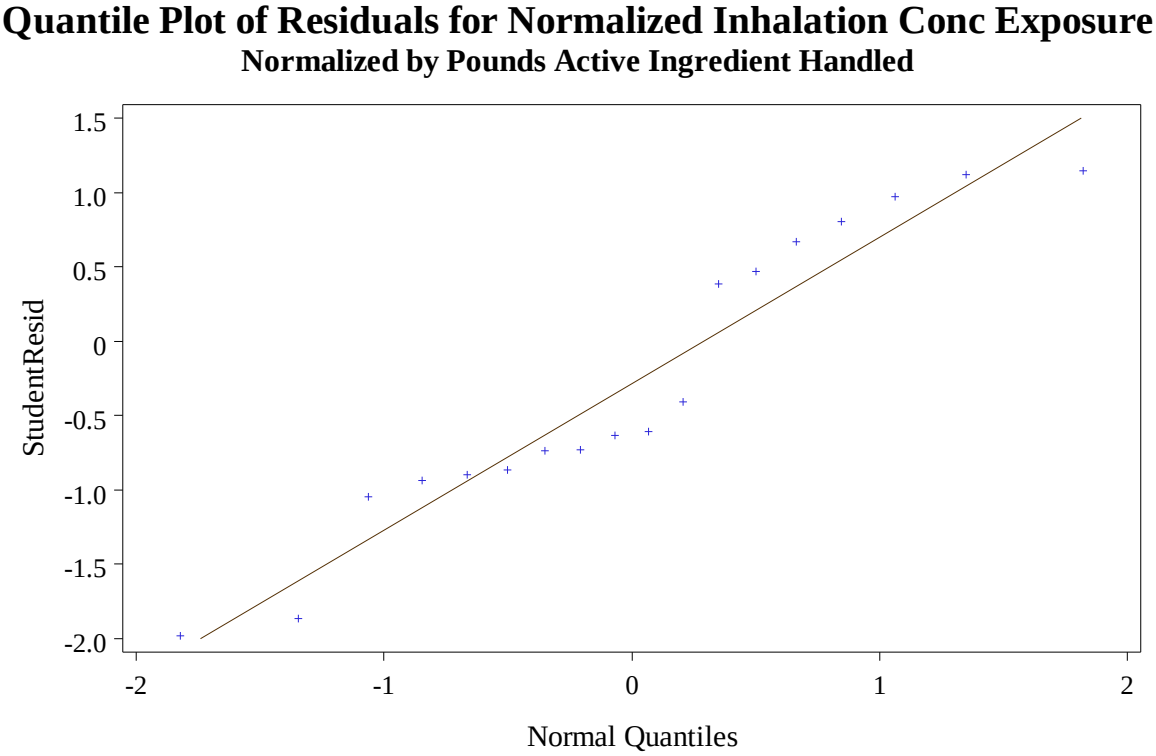

Figure 6. Quantile plot of studentized residuals for inhalation concentration exposure

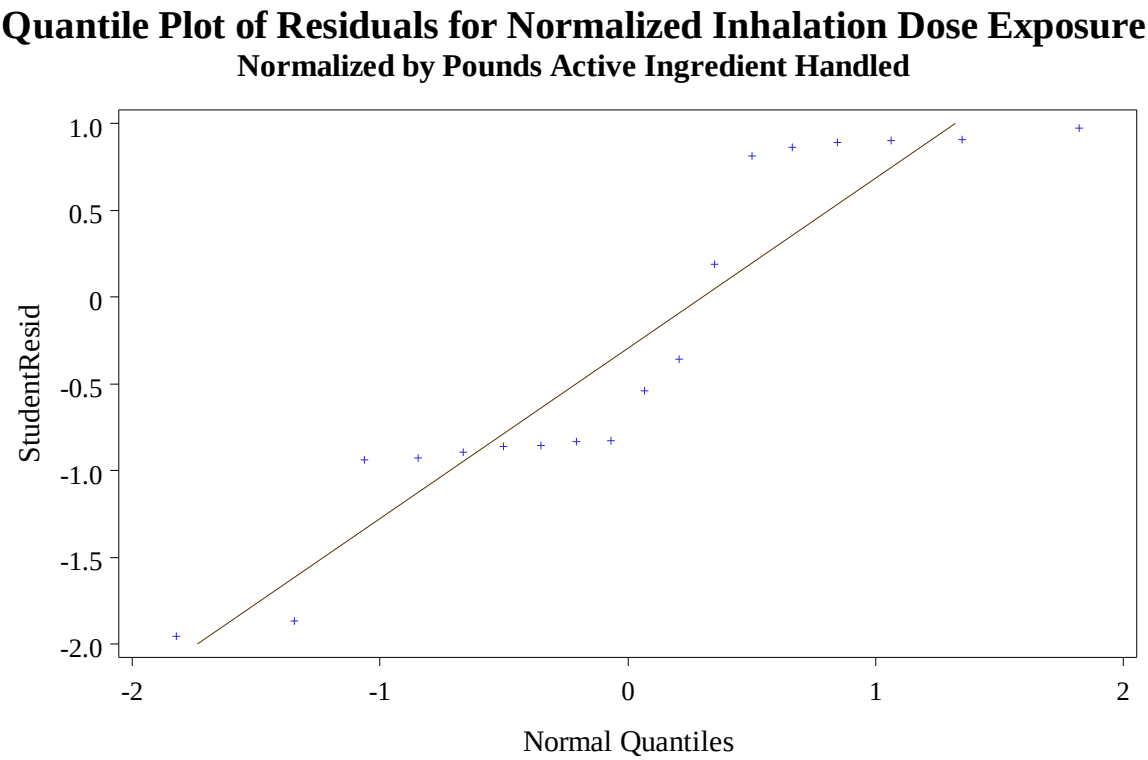

Figure 7. Quantile plot of studentized residuals for inhalation dose exposure

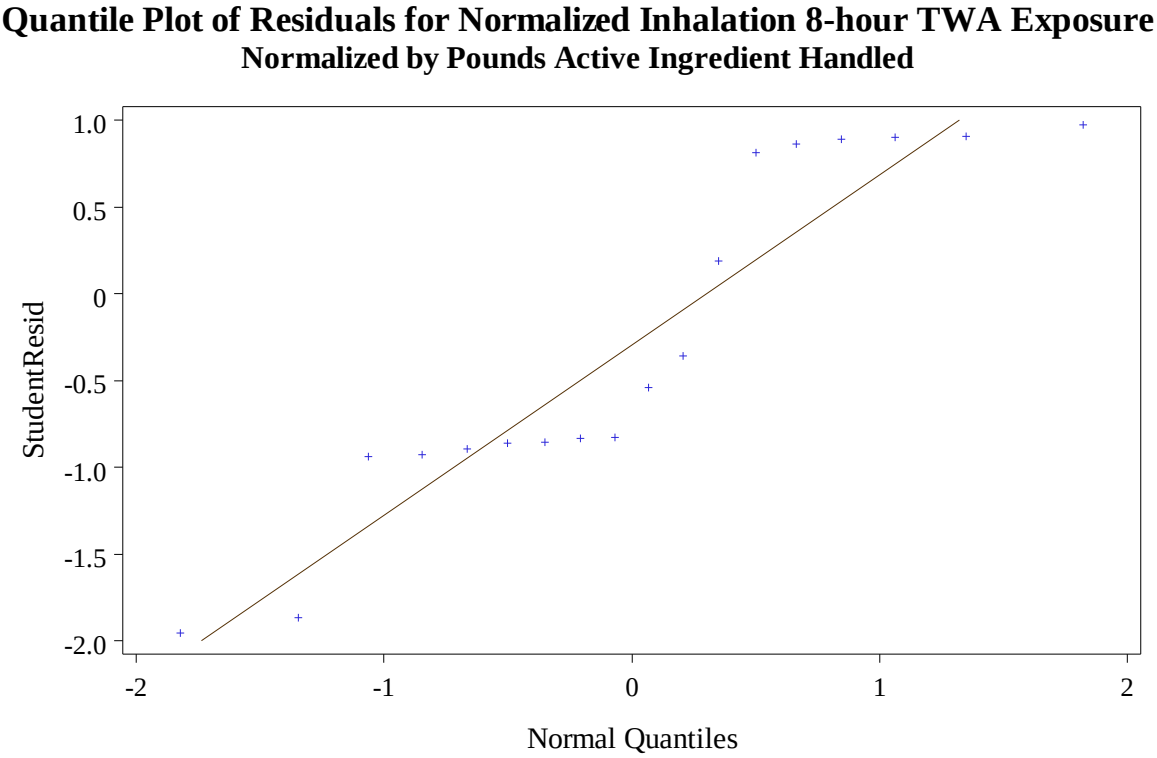

Figure 8. Quantile plot of studentized residuals for inhalation 8-hour time-weighted average exposure

The quantiles of the studentized residuals in Figures 5 and 6 appear to fit the straight line quite well, supporting the use of the lognormal mixed model for hands only and inhalation concentration exposure. The quantiles of the studentized residuals in Figures 7 and 8 for the inhalation dose and time-weighted average exposure do not appear to fit the straight line very well, suggesting concerns about the lognormal mixed model for those two cases. The large fraction of non-detects for the inhalation exposure data make the quantile plots of the studentized residuals difficult to interpret since in each study year many of the residues have the same substituted value, the flow rates are almost constant (at 2 Lpm), and the sampling durations are all between 11 and 15 minutes except for the three measurements from 2012 that ranged from 17 to 22 minutes.

10. Log-log-Linearity Analyses and Estimated Log-log Slopes

The use of the normalized or unit exposure is based on the assumption that the exposure is proportional to the normalizing variable pounds of active ingredient handled. Exact proportionality is defined as

Exposure = K × Pounds of Active Ingredient,

where K is the proportionality constant. Exact proportionality implies that

Normalized Exposure = Exposure / Pounds of Active Ingredient = K,

so that if the pounds of active ingredient is doubled, then the exposure is exactly doubled, which is not a reasonable assumption due to the variability of exposure for any given amount of active ingredient. Instead of exact proportionality we allow for random multiplicative error terms, which do not depend on the amount of active ingredient, so that

Exposure = K × Pounds of Active Ingredient × Multiplicative Errors, or

Normalized Exposure = K × Multiplicative Errors.

Since the above quantile plots support the assumption that the normalized exposure is lognormally distributed, especially for the hands only exposure, we can take natural logarithms of both sides to get a log-log-linear model of the form

Log (Exposure) = Intercept + 1 × Log (Pounds of Active Ingredient) + Error Terms.

The statistical analyses of log-log-linearity, previously referred to as proportionality, is based on the following more general log-log-linear statistical model:

Linear Mixed Model

Log (Exposure) = Intercept + Slope × Log (Pounds of Active Ingredient) + Study Year Error + Random Error.

The Study Year Error terms (one for each study year) are assumed to be normally distributed with a mean of zero and a variance of Varyear. The Random Error terms are assumed to be normally distributed with a mean of zero and a variance of Varerror. These error terms are assumed to be statistically independent of each other. The error terms are also assumed to be independent of the amount of active ingredient, which is the explanatory variable in this mixed regression model. The values of Intercept, Slope, Varyear, and Varerror are parameters of the fitted model. This linear mixed model is for the Exposure rather than the Normalized Exposure (Exposure / AI).

Using this model, taking exponentials of both sides gives

Exposure = $e^{\text{Intercept}} \times (\text{Pounds of Active Ingredient})^{\text{Slope}} \times e^{\text{Study Year Error + Random Error}}$, so that

E{Exposure | AI} = Expected Exposure Given the Pounds of Active Ingredient

= C × (Pounds of Active Ingredient)$^{\text{Slope}}$, where

C = Expected Value $\{e^{\text{Intercept}} \times e^{\text{Study Year Error + Random Error}}\} = e^{\text{Intercept}} \times e^{(\text{Varyear} + \text{Varerror})/2}$

The value of E{Exposure | AI} is the arithmetic mean of the distribution of exposures for a future set of randomly selected workers that are all pouring exactly the same amount of active ingredient, AI, into trigger spray bottles. The parameters Intercept, Varyear, and Varerror are unknown, but are estimated by fitting the linear mixed model to the Bottle scenario data.

Therefore, the expected exposure given the AI will be proportional to the pounds of active ingredient if and only if the Slope in the linear mixed model equals 1. Note that the proportionality constant is C, which is very different to the estimated value of Slope.

Lognormal Mixed Model

If the value of Slope in the linear mixed model is 1, then

Log (Exposure) = Intercept + 1 × Log (Pounds of Active Ingredient) + Study Year Error + Random Error,

so that

Log (Normalized Exposure) = Log(Exposure / Pounds of Active Ingredient)

= Intercept + Study Year Error + Random Error,

This statistical model is exactly the same as the lognormal mixed model that was defined above.

The same calculations that we used for the linear mixed model give

E{Exposure | AI} = Expected Exposure Given the Pounds of Active Ingredient

= C* × (Pounds of Active Ingredient), where

$C^* = \text{Expected Value}\{e^{\text{Intercept}^*} \times e^{\text{Study Year Error + Random Error}}\} = e^{\text{Intercept}^*} \times e^{(\text{Varyear}^* + \text{Varerror}^*)/2}$

These parameters are shown with asterisks to emphasize that they will in general be different from the ones for the model with a slope parameter not necessarily equal to 1.

Test for log-log-linearity

Proportionality or log-log-linearity of exposure to the pounds of active ingredient is statistically modeled by assuming a Slope equal to 1 in the linear mixed model.

Possible alternative models include the same formulation with a Slope of zero, implying that the exposure does not depend upon the amount of active ingredient handled, even though the amount of active ingredient handled varied between the subjects as part of the study design. Other possible models include the same model with a slope not equal to zero or one, the quadratic models discussed below, or models with more complicated relationships between the exposure and the experimental conditions. To evaluate and test whether the slope is zero, one, or other possible values, we fitted the above linear mixed model and computed confidence intervals for the slope.

The calculation of the confidence intervals for the slope depends upon the value of the denominator degrees of freedom for the linear mixed model used. A review of the alternative methods for calculating the denominator degrees of freedom for fixed effects in a mixed model using the SAS MIXED procedure is given in an article by Schaalje et al[1]. Based on that article, the following Table 13 summarizes the five available methods:

Table 13. SAS Methods for Computing the Fixed Effects Denominator Degrees of Freedom in PROC MIXED

DDF Method	SAS Abbreviation	Comments
Residual	residual	Uses residual degrees of freedom. Ignores covariance structure as defined by the RANDOM and REPEATED statements. This method is not recommended.
Containment	contain	Default method when RANDOM statements are present. Accounts for the minimum contribution of the random effects that syntactically contain the fixed effects of interest.

[1] Schaalje, G. B., J. B. McBride, G. W. Fellingham. "Approximations to Distributions of Test Statistics in Complex Mixed Linear Models Using SAS® Proc MIXED" *Proceedings of the Twenty Sixth Annual SAS Users Group International Conference*. April 2001. Long Beach, CA. ISBN 1-58025-864-6. SAS Institute, Cary, NC 27513.

DDF Method	SAS Abbreviation	Comments
Between-Within	bw	Default method when REPEATED statements are present and RANDOM statements are not present. Only exact when the data are balanced and the design is a repeated measures design with compound symmetry, and where the levels of the within-subjects effects are not replicated within any of the subjects. Otherwise the method is at best approximate and can be unpredictable.
Satterthwaite / Fai-Cornelius	satterth	Designed to approximate the denominator degrees of freedom for split-plot designs with complicated covariance structures and/or unbalanced data sets.
Kenwood-Rogers	kr	Designed to approximate the denominator degrees of freedom for designs with complicated covariance structures and/or unbalanced data sets. Results from simulations suggest better performance than the Satterthwaite method. If a covariance parameter has zero variance then this method ignores that covariance.

To interpret this table for this study, note that the RANDOM statement was used to define the study year effect. If the ICC equals zero, then there is no study year clustering and the study year variance equals zero. A balanced data set is one where each treatment combination is applied to the same number of subjects. For this study, this implies that there are the same number of workers in each study year, which was not true. Based on this summary, the recommended method is the Kenwood-Rogers method. The confidence intervals for the regression coefficients presented in this memorandum follow these recommendations. Note that this issue does not impact the calculated confidence intervals for the summary statistics in Tables 9 to 12, since they were based on a bootstrap method.

Table 14 shows the 95% confidence intervals for the slope calculated from the above linear mixed model. A confidence interval that includes one but not zero supports the assumptions of the lognormal mixed model. A confidence interval that includes zero but not one suggests that the exposure does not depend on the amount of active ingredient handled. A confidence interval that includes both zero and one suggests that either the basic statistical model is incorrect or there are not enough data to statistically infer whether the slope is zero or one. Note that, because the inhalation dose measured on the OVS tube is mathematically an exact multiple of the corresponding inhalation TWA measured on the OVS tube, the estimated slopes and confidence intervals are exactly the same. As discussed above, there were two MEs where the measured hands only exposure was unusually high compared to other measurements and so the slope estimates for hands only exposures were computed with and without these potential outliers.

For the dermal (hands only) exposure analyses there were no non-detects. Slope estimates were calculated using all the 18 MEs and also after excluding the two potential outliers.

For the inhalation exposure, 14 of the 18 MEs were non-detects. The rows marked “Substitute ½ LOQ” calculate the slope estimates after replacing each non-detect residue by half the LOQ. The rows marked “Censored data MLE” calculate the slope estimates using a censored maximum likelihood statistical method described in the following paragraph:

The mixed linear model fitted to the unit exposures from the censored and uncensored liquid pour exposure data has the form:

Log (Exposure) = Intercept + Slope × Log(Pounds of Active Ingredient) + Year + Error.

In this model, Slope is an unknown parameter, Year is a normally distributed random effect variable with independent, identically distributed values for each study year, and Error is a normally distributed error variable with independent, identically distributed values for each total exposure measurement. This model was fitted using the SAS procedure NLMIXED, using code adapted from the article "Analysis of Lognormally Distributed Exposure Data with Repeated Measures and Values below the Limit of Detection Using SAS" (YAN JIN, MISTY J. HEIN, JAMES A. DEDDENS and CYNTHIA J. HINES, Ann Occup Hyg (2011) 55(1): 97-112, doi:10.1093/annhyg/meq061). For these calculations, the marginal likelihood averaged over the random effects is maximized. The fitted model has values for the following parameters: the intercept, slope, Variance of Year, Variance of Error.

Table 14. 95 percent confidence intervals for the slope of log exposure versus log pounds active ingredient handled with and without the potential outlier hands only dermal exposure data for Reduced Splash ME 1 in group 1a in 2012 and ME 8 in 2014

Exposure Route	Treatment of Non-detects	Data	Estimate	Lower	Upper
Hands Only Dermal (mg)	N/A	All 18 Values	0.90	0.36	1.45
	N/A	Exclude outlier data	0.93	0.39	1.48
Inhalation Concentration (mg/m^3)	Substitute ½ LOQ	All 18 Values	0.37	0.14	0.61
	Censored data MLE	All 18 Values	0.96	-20.43	22.36
Inhalation Dose (mg)	Substitute ½ LOQ	All 18 Values	0.41	0.17	0.64
	Censored data MLE	All 18 Values	1.28	-29.28	31.84
Inhalation 8-hour TWA (mg/m^3)	Substitute ½ LOQ	All 18 Values	0.41	0.17	0.64
	Censored data MLE	All 18 Values	1.28	-29.28	31.84

For the hands only dermal exposure, the estimated slope is about 0.9 (with or without the outliers) and the confidence interval for the slope includes 1 but not 0. Thus, for these cases, the assumption of independence was rejected and the assumption of log-log-linearity with slope 1 was not rejected.

For all the inhalation exposure cases using the half LOQ substitution method, the confidence interval for the slope lies between 0 and 1 and so does not include 0 or 1. Thus, for these cases, the assumption of independence was rejected and the assumption of log-log-linearity with a slope of 1 was also rejected. However, these results strongly rely on the substitution methods used to deal with the non-detects. The more general censored MLE method produces slope estimates of either 0.96 or 1.28 with extremely wide confidence intervals since in most cases the inhalation exposure is only known to be in a wide interval, so that it is very uncertain as to whether the slope is positive or negative.

The lognormal mixed model regression results are shown in Figures 9 to 12, using all the data (including the potential hands only exposure outliers) and the half LOQ substitution method for inhalation exposure. The scatter plots show the data points and the fitted regression lines. The data points on the left hand sides of the graphs (close to a logarithm of −7.5) are for a concentration of 0.02% AI (measured in 2014) and the data points on the right hand sides of the graphs (close to a logarithm of −5.5) are for a concentration of 0.2% AI (measured in both 2012 and 2014).

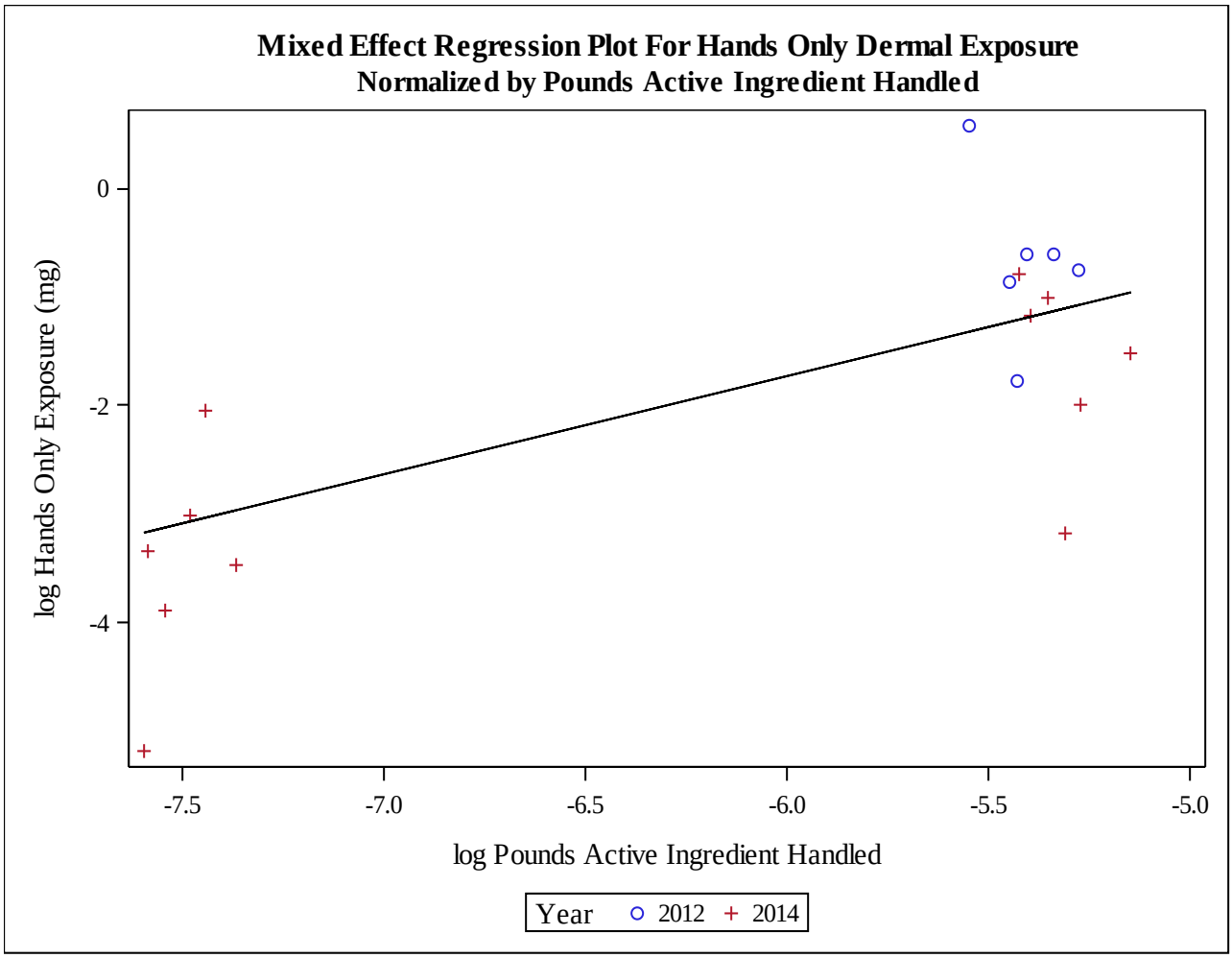

Figure 9. Mixed effect regression plot for hands only

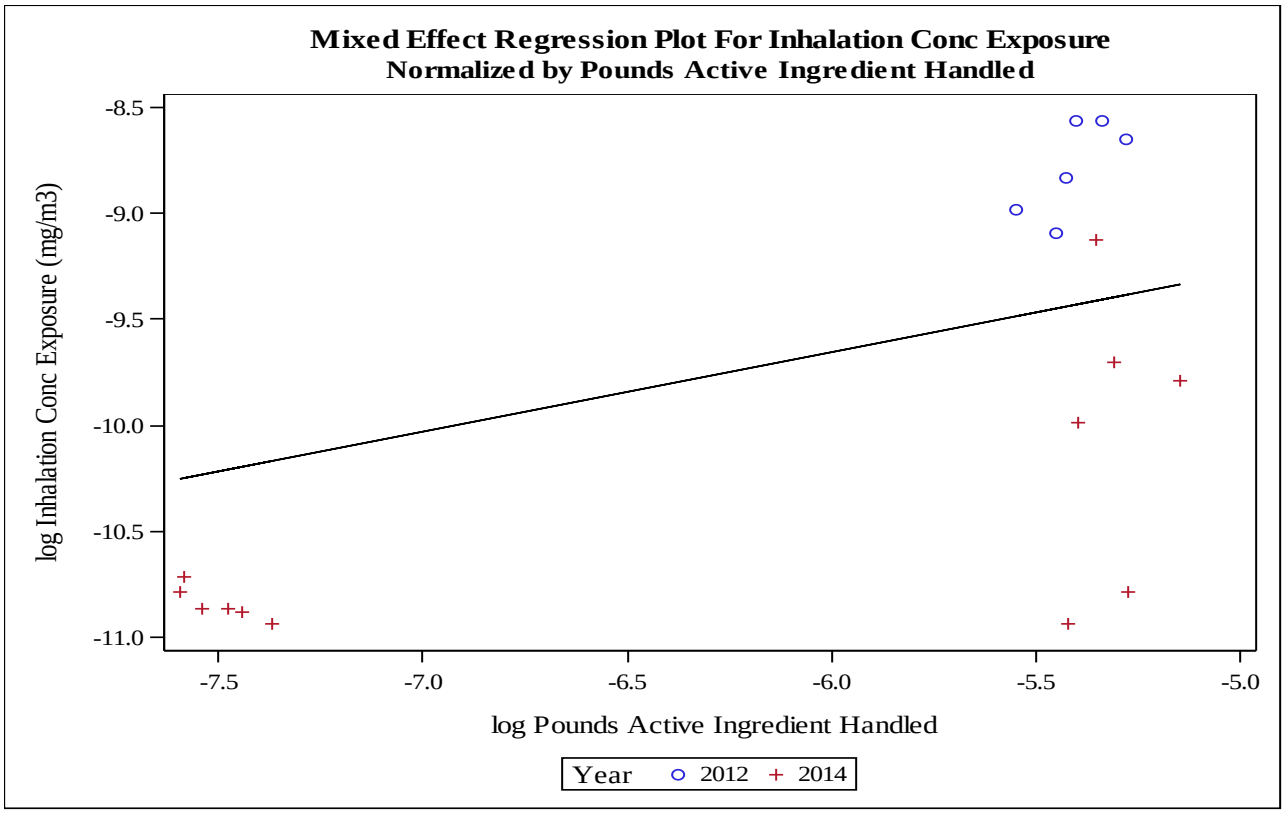

Figure 10. Mixed effect regression plot for inhalation concentration

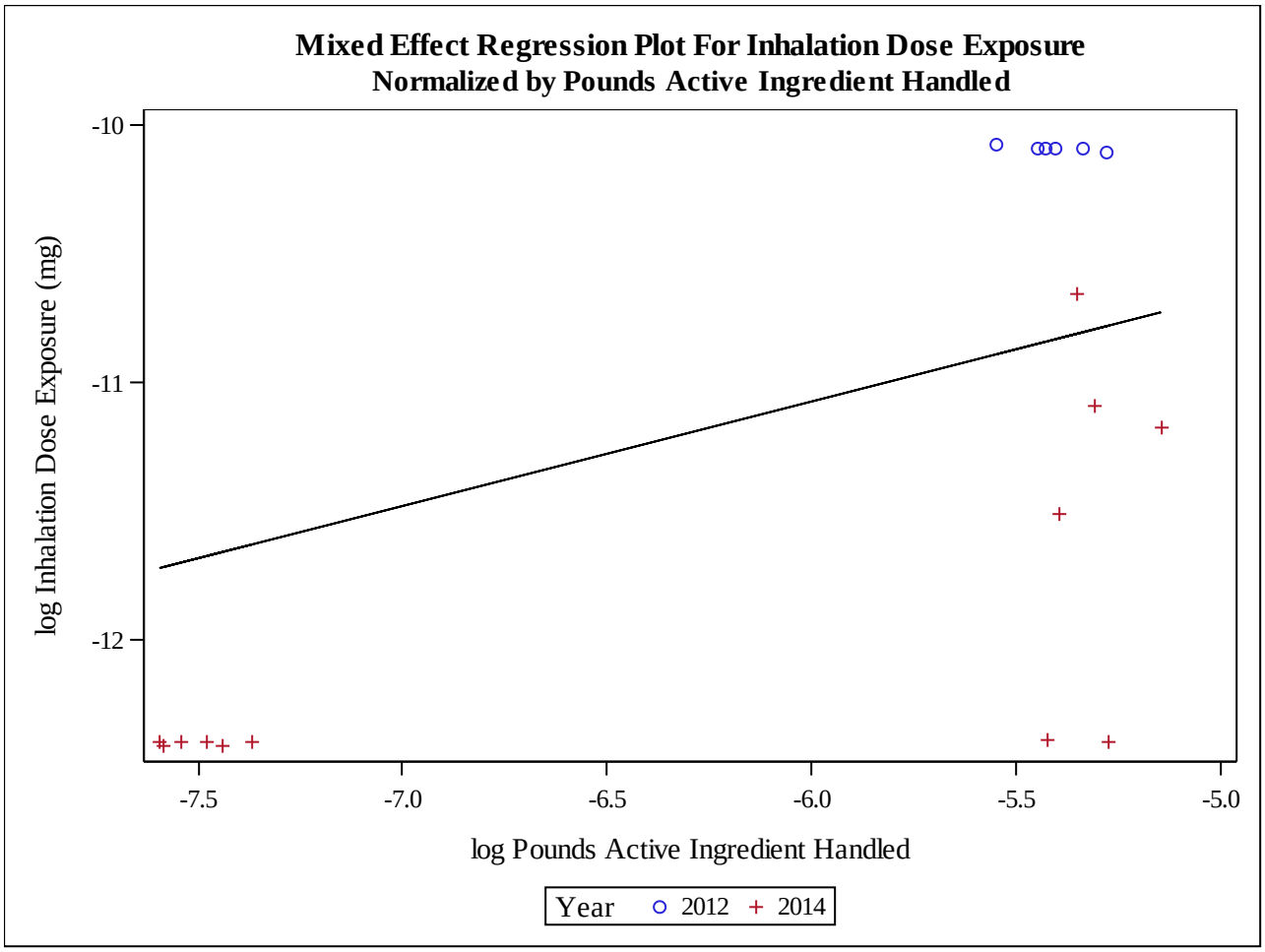

Figure 11. Mixed effect regression plot for inhalation dose

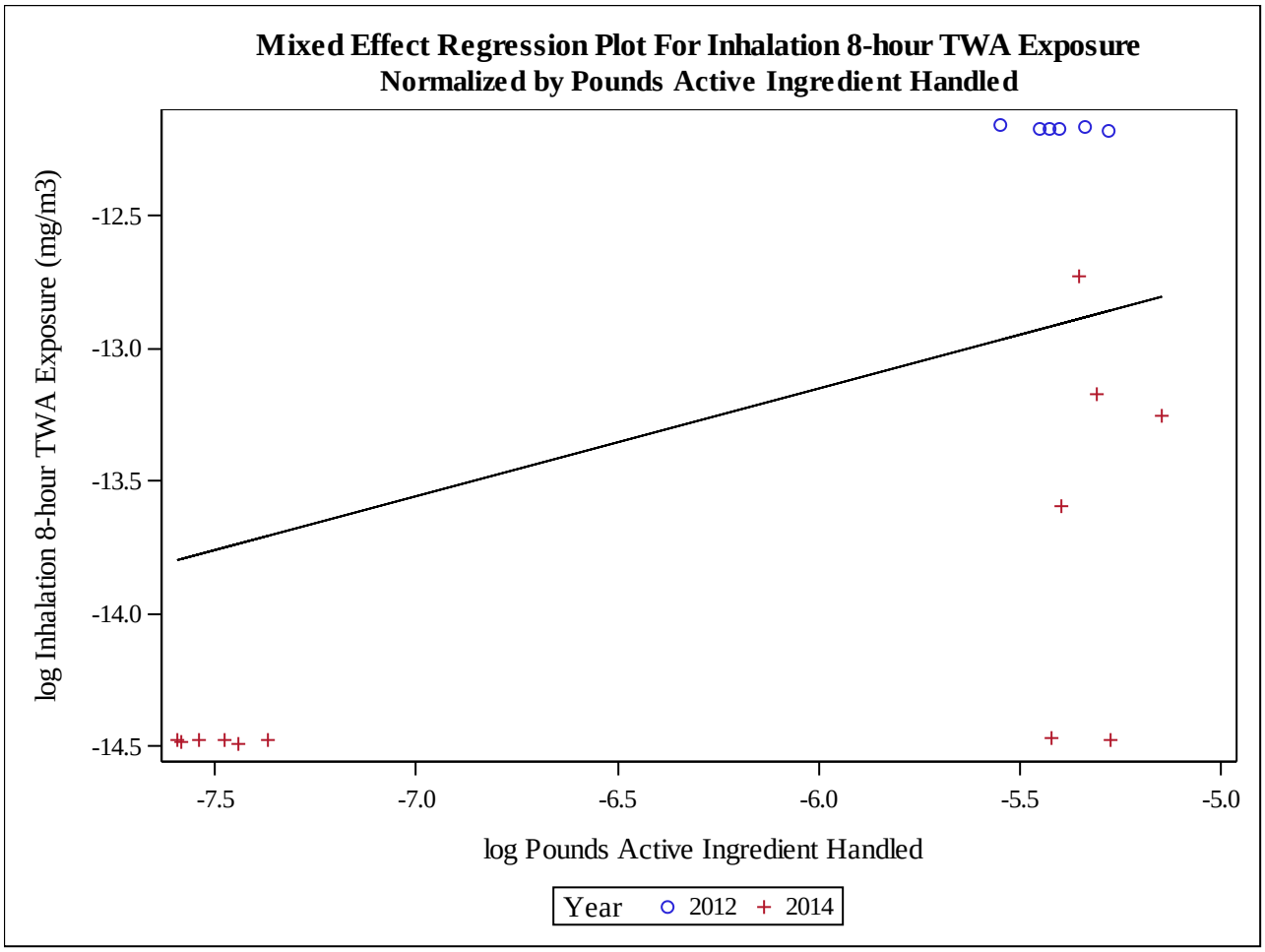

Figure 12. Mixed effect regression plot for inhalation 8-hour time weighted average

11. Quadratic models

The log-log-linearity test was based on a linear model for log exposure versus log pounds active ingredient handled. The HSRB suggested that a quadratic model should also be considered.

There are two quadratic models that could be considered. Since the original linear model is of the form

$$\text{Log (Exposure)} = \text{Intercept} + \text{Slope} \times \text{Log (Pounds of Active Ingredient)} + \text{Error Terms},$$

the main quadratic model is of the form

$$\text{Log (Exposure)} = \text{Intercept} + \text{Slope} \times \text{Log (Pounds of Active Ingredient)} + \text{Quad} \times \{\text{Log (Pounds of Active Ingredient)}\}^2 + \text{Error Terms}.$$

Note that the quadratic term is the square of the logarithm of the pounds of active ingredient rather than the logarithm of the square; the latter approach produces an ill-defined model with two multiples of the logarithm of the pounds of active ingredient.

Another approach might be to consider a quadratic model for exposure:

$$\text{Exposure} = \text{Intercept} + \text{Slope} \times (\text{Pounds of Active Ingredient}) + \text{Quad} \times (\text{Pounds of Active Ingredient})^2 + \text{Error Terms}.$$

We do not recommend this second approach for these data since the exposures are known to be non-negative and the quantile plots for hands only exposure data are better modeled using a log-normal distribution than using a normal distribution. Furthermore, unless the intercept is zero, this model predicts a nonzero exposure when the pounds of active ingredient is zero, and so a more realistic (though possibly poorer-fitting) model of this form would have a zero intercept. For other exposure data a log-log-linearity test could be carried out by fitting the zero intercept model

$$\text{Exposure} = \text{Slope} \times (\text{Pounds of Active Ingredient}) + \text{Quad} \times (\text{Pounds of Active Ingredient})^2 + \text{Error Terms}$$

and testing if Quad equals zero.

The parsimony principle suggests that the appropriate statistical procedure for this study is to first fit the quadratic regression model for the logarithm of the exposure

$$\text{Log (Exposure)} = \text{Intercept} + \text{Slope} \times \text{Log (Pounds of Active Ingredient)} + \text{Quad} \times \{\text{Log (Pounds of Active Ingredient)}\}^2 + \text{Error Terms}.$$

If the coefficient Quad is statistically significant at the 5% level, which is equivalent to requiring that the 95% confidence interval does not include zero, than the quadratic model is supported. Otherwise the linear model should be used.

Table 15 presents the fitted quadratic models from the study for the mixed models of four exposure measurements (Hands Only, Inhalation Concentration, Dose and 8-Hour TWA). In view of the earlier discussion about denominator degrees of freedom, the confidence intervals are calculated using the Kenwood-Rogers method. The intercepts are not shown. These calculations use all the data for hands only exposure and the half LOQ substitution method for inhalation exposure.

Table 15. Quadratic mixed models with 95% confidence intervals for the log exposure versus log pounds active ingredient handled

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Hands Only	Slope	-30.97	14.05	-65.17	3.23	2.35	0.07	68.41
Hands Only	Quad	-2.49	13.91	-5.18	0.19	2.35	0.07	5.37
Inhalation Conc	Slope	6.63	14.15	-8.23	21.48	2.89	0.85	29.71
Inhalation Conc	Quad	0.49	14.16	-0.67	1.65	2.89	0.85	2.32
Inhalation Dose	Slope	2.59	14.13	-12.50	17.69	3.12	0.86	30.19
Inhalation Dose	Quad	0.17	14.14	-1.01	1.35	3.12	0.86	2.36
Inhalation TWA	Slope	2.59	14.13	-12.50	17.69	3.12	0.86	30.19
Inhalation TWA	Quad	0.17	14.14	-1.01	1.35	3.12	0.86	2.36

Since the 95% confidence intervals for Quad include zero in every case, the quadratic coefficient is not statistically significant and the quadratic models are not supported.

12. Threshold Analyses

As shown above, two mixed models were fitted to the dermal and inhalation exposure data and can be used to estimate the conditional mean exposure, i.e., the expected exposure conditional on the amount of active ingredient, E{Exposure | AI}.

Linear Mixed Model

Log (Exposure) = Intercept + Slope × Log (Pounds of Active Ingredient) + Study Year Error + Random Error,

which implies

Equation 1: E{Exposure | AI} = Expected Exposure Given the Pounds of Active Ingredient $= C \times AI^{Slope}$,

where

$C = e^{Intercept} \times e^{(Varyear + Varerror\}/2}$.

Lognormal Mixed Model

If the value of Slope in the linear mixed model is 1, then

Log (Normalized Exposure) = Log(Exposure / Pounds of Active Ingredient)

= Intercept* + Study Year Error + Random Error,

which implies

Equation 2: E{Exposure | AI} = Expected Exposure Given the Pounds of Active Ingredient = C* × AI,

where

$C^* = e^{Intercept^*} \times e^{(Varyear^* + Varerror^*)/2}$.

(The parameters for the lognormal mixed model are asterisked). If Slope equals 1 then the two models are identical.

These two statistical models can be compared by calculating the threshold value of the pounds of active ingredient at which both models predict the same conditional mean exposure.

Define Threshold = $\left(\frac{C}{C^*}\right)^{\frac{1}{1-Slope}}$.

Thus E(X | AI) for the lognormal mixed model > E(X | AI) for the linear mixed model if and only if

$C^* \times AI > C \times AI^{Slope}$, which is true if and only if

Either Slope < 1 and AI > Threshold

Or Slope > 1 and AI < Threshold.

These are the conditions under which the lognormal mixed model overestimates exposure compared to the linear mixed model.

The most useful case is when slope < 1. If so, the lognormal mixed model is "more conservative" (i.e., predicts higher exposure) when the pounds of active ingredient is high (more specifically, above the threshold). When the pounds of active ingredient is below the threshold, then either the linear mixed model equation $C \times AI^{Slope}$ can be used to estimate the conditional mean exposure, or instead one can use the upper bound C* × Threshold. If AI = Threshold, then the estimates of the conditional mean exposure are the same.

The Threshold values are tabulated in Table 16, calculated using all the dermal hands only measurements and substituting non-detected inhalation exposure values using half the LOQ.

We now have two estimates of the conditional mean exposure for a given amount of active ingredient, equations 1 and 2. The graphs in Figures 13 to 16 below compare the conditional mean exposure estimates for the hands only dermal and for the three inhalation exposure metrics, respectively. The conditional mean exposure is plotted against the pounds of active ingredient. The purple curve gives the estimates for the linear mixed model in equation 1. The brown line gives the estimates for the lognormal mixed model in equation 2. The two estimates are equal if the pounds of active ingredient equals the Threshold value.

For all these cases the estimated slope is less than 1. As proven above, the conditional mean exposure from the lognormal mixed model will be greater than the conditional mean exposure from the linear mixed model for amounts of active ingredient above the threshold (right hand side of the graph). The conditional mean exposure from the lognormal mixed model will be less than the conditional mean exposure from the linear mixed model for amounts of active ingredient below the threshold (left hand side of the graph).

Table 16. Threshold values for the amount of active ingredient

Exposure Route	Clothing	Slope	Threshold Level (lb active ingredient)
Dermal (mg)	Hands only	0.90	0.00596
Inhalation Concentration (mg/m^3)		0.37	0.00364
Inhalation Dose (mg)		0.41	0.00401
Inhalation 8-hour TWA (mg/m^3)		0.41	0.00401

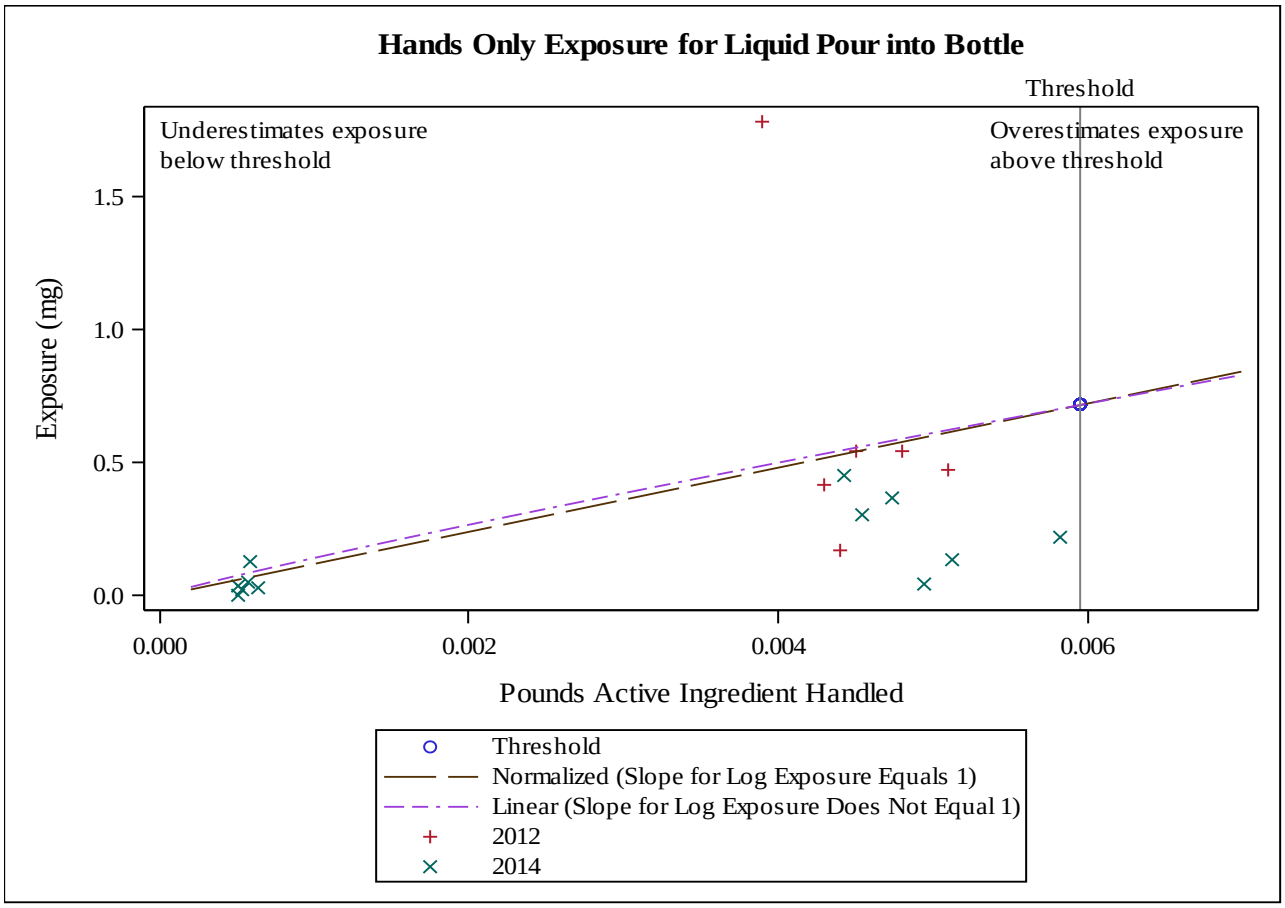

Figure 13. Threshold analyses for hands only

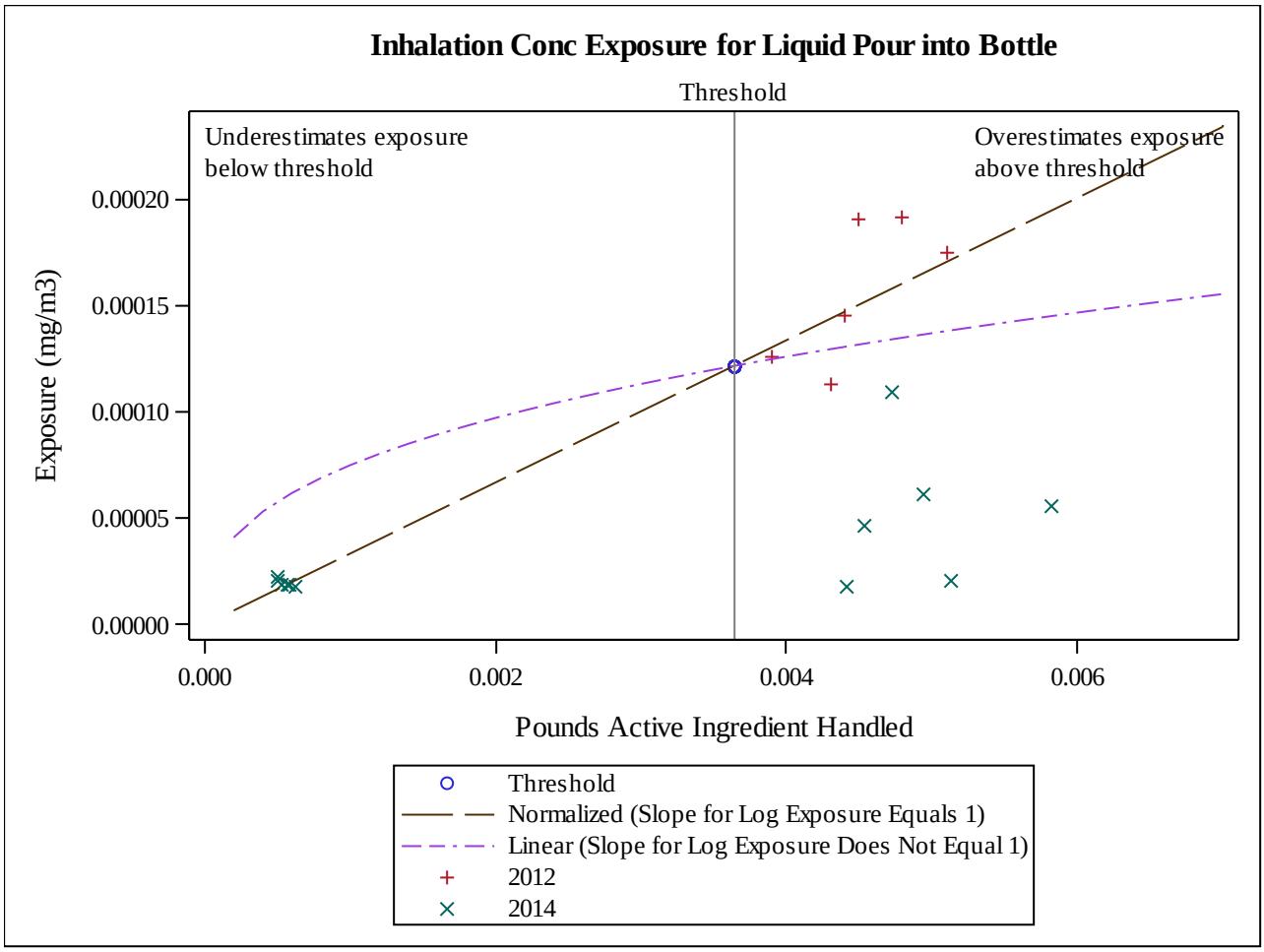

Figure 14. Threshold analyses for inhalation concentration

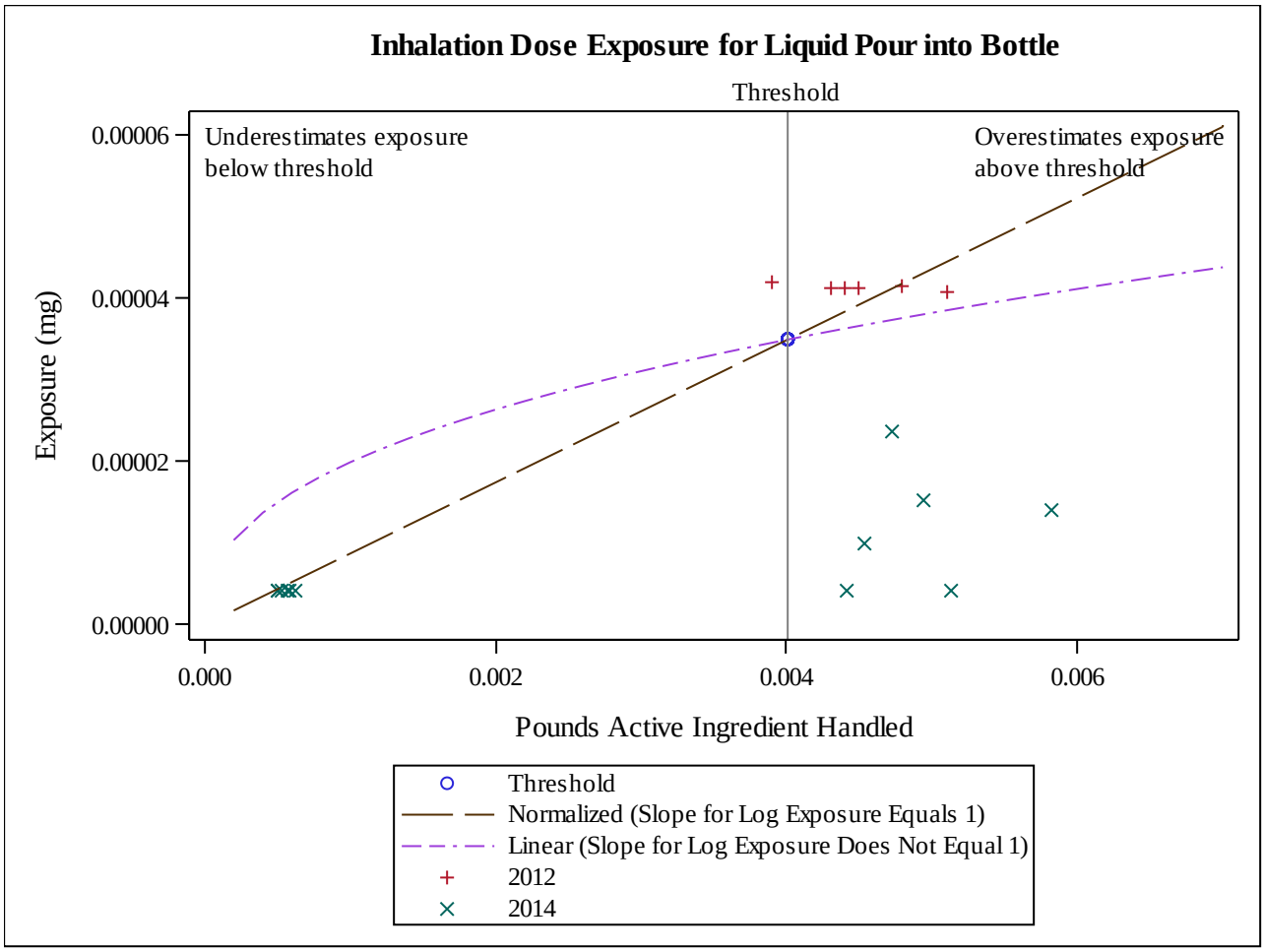

Figure 15. Threshold analyses for inhalation dose

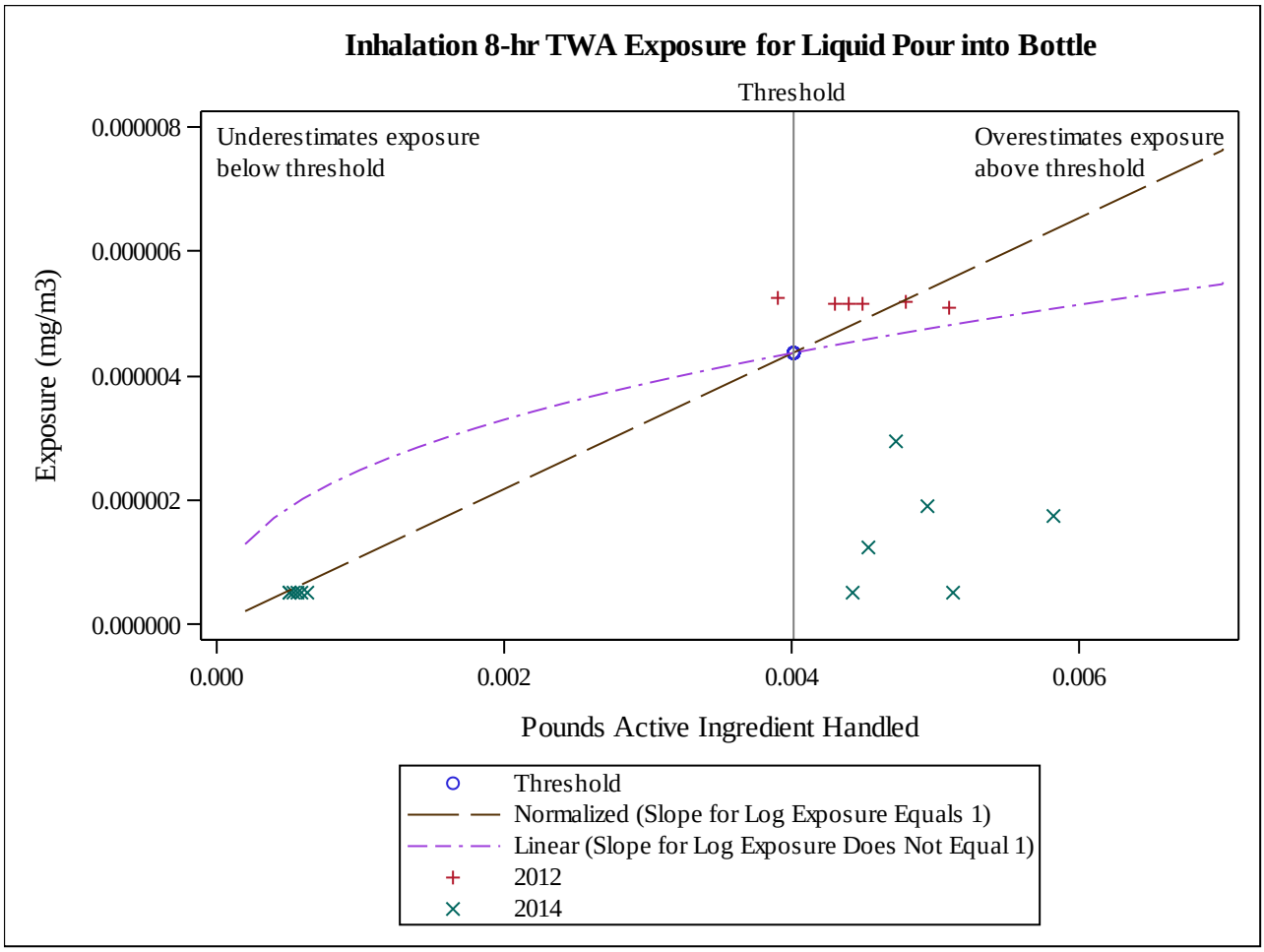

Figure 16. Threshold analyses for inhalation 8-hour time weighted average

13. Concentration Effects

An important issue that arose from the analyses of the original liquid pour study and of some of the earlier AEATF studies is the validity of the assumption that the exposure is primarily driven by the mass of active ingredient rather than the volume poured or the chemical concentration. Partly for this reason, the 2014 supplemental study had six MEs at the same 0.2% concentration as the 2012 study and another six MEs at a concentration of 0.02%. Thus the combined study had data at two concentration levels. For the Bottle scenario, all the workers were asked to fill 10 trigger spray bottles with 4 fluid ounces per bottle, so the volumes poured were almost constant for all the workers and an analysis of the effect of volume poured on exposure is not viable. Therefore, the pounds of active ingredient was also almost constant for each concentration level, at about 0.0050 pounds (ranging from 0.0039 to 0.0058) at the 0.2% concentration level and about 0.0005 pounds (ranging from 0.00050 to 0.00059) at the 0.02% concentration level. An additional complication is that the 2012 data was only at the high concentration level, whereas the 2014 data was at both levels, which it makes it difficult to statistically distinguish effects of mass amounts, concentrations, and study year.

To evaluate this issue we fitted a version of the lognormal mixed model with different intercepts for the two concentrations:

Log (Normalized Exposure) = Log(Exposure / Pounds of Active Ingredient)

= Intercept1 + Study Year Error + Random Error, if concentration = 0.2%,

= Intercept2 + Study Year Error + Random Error, if concentration = 0.02%.

As before, Study Year Error is a normally distributed random effect for the study year, Random Error is an independent normally distributed random error term for each ME. The intercepts Intercept1 and Intercept2 depend upon the concentration level (0.2% or 0.02%). We tested whether the difference between the two intercepts, Intercept1 – Intercept2, was statistically significantly different from zero, which would imply that the normalized exposure is affected by the concentration. Equivalently, a statistically significant different implies that the exposure is affected by the concentration after adjusting for the effects of the amount of active ingredient.

The p-vales are shown in Table 17. P-values below 0.05 show a statistically significant effect of concentration at the 5% significance level. The effect was not significant for hands only dermal (p-value = 0.77). A similar p-value was found after excluding the two potential outliers mentioned above. The effect was highly significant (p-value < 0.0001) for the inhalation exposure metrics. However, those inhalation exposure results are not regarded as being very reliable because of the impact of the large number of non-detects that were substituted by half the LOQ: For example, the inhalation concentration data in 2012 were all measured at a concentration of 0.2% and all the measured values were below the LOQ of 10 ng, leading to an average inhalation concentration of 0.00016 mg/m^3. In 2014, the LOQ was reduced to 1 ng, and 4 of the 6 measurements at a concentration of 0.2% were below this lower LOQ, leading to an average inhalation concentration of 0.00005 mg/m^3. Had the unknown true measurements in 2012 been comparable to the 2014 data at the same liquid concentration, the estimated incremental impact of the liquid concentration level would have been much smaller.

Table 17. P-values for testing exposure effects due to concentrations after adjusting for the amount of active ingredient

Exposure Route	Clothing	P-value
Dermal (mg)	Hands only	0.765
Inhalation Concentration (mg/m^3)		0.000041
Inhalation Dose (mg)		0.000069
Inhalation 8-hour TWA (mg/m^3)		0.000069

14. Alternative Statistical Approaches

Finally, we briefly discuss some alternative statistical approaches that were suggested by the HSRB (in their review of the solid pour study protocol) but we chose not to implement here.

For estimating the 95th percentile of the normalized or unit exposure, our preferred approach is to fit a mixed statistical model that includes a random study year effect as well as the random error. HSRB recommended consideration of a quantile regression approach, which would provide confidence intervals for the 95th percentile assuming a simple random sample from an unspecified distribution. The quantile regression approach could also be applied to the exposure to estimate the 95th percentile of the exposure as a linear or non-linear function of the amount of active ingredient. We chose not to apply these approaches here because of the finding of a large, though not statistically significant, ICC for the study year error which cannot be modeled using non-parametric methods.

For estimating the dependence of exposure on the amount of active ingredient, our main model was the linear mixed model described above, where the mean log(exposure) is a linear function of the log(amount of active ingredient). We also considered a quadratic model, but found the quadratic term to be non-significant. The HSRD suggested including non-linear functions of the log-log-logistic or logistic forms:

Log-log-logistic: Exposure = $\delta + \frac{\alpha - \delta}{1 + \gamma \exp\{\beta \log(AI)\}}$ + Error.

3-parameter logistic: Exposure = $\frac{C}{1 + \exp\{\alpha + \beta \times AI\}}$ + Error.

Since there is no background exposure in most of these scenarios, we can usually assume δ = 0 for the log-log-logistic model. A major problem with using the log-log-logistic model is that the mean exposure is bounded above, which is possibly unrealistic. These models could be fitted using the NLMIXED SAS procedure.

Since the linear mixed model fitted the hands only dermal data reasonably well, and since the slope was close to 1, supporting the use of the lognormal mixed model, which is more convenient to apply, we chose not to fit these more complicated models for this scenario. For the inhalation exposures, the results from fitting these more complicated models may not very reliable due to the large number of non-detects.